The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

T.G.D. CAPSTICK

DPharm

2014

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Toby Gareth David CAPSTICK

Submitted for the Degree of
Doctor of Pharmacy

School of Pharmacy, Faculty of Life Sciences
University of Bradford
2014

Abstract

Toby Gareth David Capstick

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Keywords: Asthma; Pharmacist interventions; Pharmacist prescribing; Quality of life; Asthma control; Hospital pharmacists; Community pharmacists; Care transitions.

Despite national guidelines, the management of difficult asthma remains suboptimal, and there may be opportunities for pharmacists to improve asthma outcomes. This six-month prospective, randomised, open study investigated the effects of pharmaceutical care across primary and secondary care on difficult asthma.

Fifty-two patients attending a hospital difficult asthma clinic were randomised (1:1) to receive usual medical care (UC), or pharmacist interventions (PI) comprising asthma review, education, and medicines optimisation from a hospital advanced clinical pharmacist, plus follow-up targeted Medicines Use Review (t-MUR) from community pharmacists.

Forty-seven patients completed the study. More interventions were performed in the PI group at baseline (total 79 vs. 34, $p<0.001$), but only six patients received a t-MUR. At six-months, PI were non-inferior to UC for all outcomes. The primary outcome measure was Juniper's Asthma Control Questionnaire score and reduced (improved) from a median (IQ) score of 2.86 (2.25, 3.25) and 3.00 (1.96, 3.71) in the PI and UC groups respectively to 2.57 (1.75, 3.67) and 2.29 (1.50, 3.50).

At baseline, 58.8%, 46.9% and 17.6% of patients had optimal inhaler technique using Accuhalers, Turbohalers or pMDIs; education improved technique but this was not maintained at six-months. Adherence rates <80% were observed in 57.5% of patients at baseline, and was improved in the PI group at six-months (10/20 PI vs. 3/21 UC had adherence rates of 80-120%, $p=0.020$).

This study demonstrates that the management of difficult asthma by specialist pharmacists is as effective as usual medical care. Future research should investigate whether pharmacist-led follow-up produces further improvements.

Acknowledgements

I would like to thank my research supervisors Professor Alison Blenkinsopp, Dr Julie Morgan and Dr Jon Silcock, and my clinical supervisor Dr Ian Clifton.

I would also like to thank all the staff working in the Leeds Difficult Asthma Clinic and the Community Pharmacists in Leeds who were involved in the study.

This study was sponsored by a research grant from The Pharmaceutical Trust for Educational and Charitable Objects (PTECO) (now known as Pharmacy Research UK).

Juniper's Asthma Control Questionnaire and Asthma Quality of Life Questionnaire were used with permission of Professor Elizabeth Juniper. The European Quality of Life-5 Questionnaire was used with permission of the Euroqol Group Foundation. The Beliefs about Medicines Questionnaire and Medical Adherence Report Scale were used with permission of Professor Rob Horne.

Dedicated to my fiancée Charlotte, who has supported me throughout this research project.

Table of Contents

List of Figures

List of Tables

Glossary

A&E	Accident and Emergency department
ACC	Accuhaler
ACQ	Juniper's Asthma Control Questionnaire
ACT	Asthma Control Test
AQLQ	Juniper's Asthma Quality of Life Questionnaire
AQLQ(S)	Standardised Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
BMQ	Beliefs about Medicines Questionnaire
BTS	British Thoracic Society
CBCT	Cognitive-based behaviour change techniques
CCM	Chronic Care Model
CI	Confidence Intervals
COPD	Chronic obstructive pulmonary disease
DPI	Dry Powder Inhaler
EB	Easi-Breathe
EH	Easyhaler
EQ-5D-5L	European Quality of Life-5 Dimensions Questionnaire
ERS	European Respiratory Society
FeNO	Exhaled nitric oxide
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GP	General Practitioner
HH	HandiHaler
HIV	Human immunodeficiency virus
ICS	Inhaled corticosteroid
IFR	Inspiratory Flow Rate
IQ	Interquartile
LABA	Long-acting $beta_2$-agonist
LAMA	Long -Acting Muscarinic Antagonist
LKTa	Leukotriene receptor antagonist
LWAQ	Living with Asthma Questionnaire
MARS	Medication Adherence Report Scale

MDISM	MDI + spacer (multiple-breath method)
MDISS	MDI + spacer (single-breath method)
MUR	Medicines Use Review
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroid
PEF	Peak Expiratory Flow
PI	Pharmacist Intervention
pMDI	Pressurised Metered Dose Inhaler
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RSP	Respimat
SABA	Short-acting $beta_2$-agonist
SD	Standard Deviation
SF-36	Short Form-36
SIGN	Scottish Intercollegiate Guidelines Network
t-MUR	Targeted Medicines Use Review
TDM	Therapeutic drug monitoring
TH	Turbohaler
UC	Usual Care
VAS	Visual Analogue Scale
VCD	Vocal cord dysfunction
WHO	World Health Organisation

1 Executive Summary

1.1 Introduction

Asthma is a condition that is characterised by variable expiratory airflow obstruction resulting from chronic airway inflammation producing characteristic symptoms of wheeze, breathlessness, chest tightness and cough that vary over time and intensity (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014).

There are an estimated 5.4 million people with asthma in the UK (National Institute for Health and Care Excellence, 2013), and the majority of adults can be successfully treated with low to moderate inhaled corticosteroid doses at Steps 1 to 3 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines. It is estimated that about 13.8% of patients in the UK are treated at Steps 4 and 5 of the BTS Asthma guidelines (Hoskins et al., 2000). Approximately half of these are thought to be inadequately controlled by maximal inhaled and oral therapies (Hoskins et al., 2000), and are labelled as having ‘difficult asthma’ (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014).

The aim of asthma treatment is to achieve and maintain asthma control and normal activity levels, and to minimise the future risk of exacerbations, fixed airflow limitation and adverse effects (Global Initiative for Asthma, 2014, British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). Whilst this is achievable for most patients, those with difficult asthma are more complex and require referral to specialist hospital services led by consultant physicians in order to improve patient outcomes (NHS England, 2013). The goal of difficult asthma management is frequently to stabilise the condition and to maintain the highest level of asthma control and quality of life as possible rather than achieving total asthma control, which may not be achievable in all patients.

The Royal College of Physicians recently published a report from a national investigation into asthma deaths in the UK between February 2012 and January 2013 (Royal College of Physicians, 2014). This identified a number of deficiencies in asthma care including lack of asthma action plans, sub-optimal use of preventer inhalers and over use of short-acting reliever inhalers. This

report identified that pharmacists can play a key role in asthma management by identifying patients who may underuse preventer inhalers or who overuse reliever inhalers, as well as assessing inhaler technique, and providing self-management education including developing personalised asthma action plans.

Previous pharmacist interventional studies have reported benefits to patients with asthma when provided with asthma education, asthma action plans, inhaler technique training, and behaviour modification. However these studies have focused on the management of asthma in patients with mild to moderate asthma symptoms, but there is minimal research in patients with difficult asthma.

The research study presented in this thesis is the first to investigate the effects of a redesigned pharmaceutical pathway across the primary and secondary care interface in patients with difficult asthma. It is also the first to compare pharmaceutical management of asthma compared to usual medical care.

1.2 Aims

To determine the effects of a co-ordinated management strategy between primary and secondary care pharmacists on asthma control and Quality of Life in patients with difficult asthma.

1.3 Objectives

The primary objective of this study is to measure the impact on asthma control on the management of difficult asthma by a Hospital Advanced Clinical Pharmacist and community pharmacist.

Secondary objectives are to determine the impact of the intervention on quality of life, exacerbations, lung function, inhaler technique and adherence.

1.4 Methods

The study was designed as a pragmatic six-month, prospective, randomised, open trial. Fifty-two patients attending a hospital difficult asthma clinic were randomised to either a usual medical care (UC) group, or pharmacist intervention (PI) group. The inclusion criteria included patients aged 18 to 70

years, with a clinical diagnosis of asthma, fulfilling the criteria for difficult asthma, who were able to speak, read and write in English, and were eligible for a Medicines Use Review (MUR). Patients were excluded if they were not responsible for taking their own medications, or failed to provide written informed consent.

Patients in the UC group received a 'usual' standard asthma review in clinic from a consultant, specialist registrar, or specialist respiratory nurse in line with standard difficult asthma clinic procedures. Patients in the PI group received an asthma review from an advanced clinical pharmacist in clinic, comprising education on asthma and medication, inhaler technique training in addition to the 'usual' standard asthma review, plus a follow-up targeted MUR (t-MUR) from their usual community pharmacist at four to eight weeks following the baseline consultation. Patients in both groups were followed up at six months.

1.5 Results

Between 25th September 2012 and 29th October 2013, 188 patients were screened for inclusion in the study and 52 were recruited. Twenty-six were randomly assigned to the PI group and 26 to the UC group. Forty-seven patients (24 in the PI group) were followed up for a median (interquartile range, IQ) of 182 (175, 203) days and were included in the intention to treat analysis. Only six participants (23%) in the PI group received a t-MUR at a mean of 60 days (range 28 – 143 days) following randomisation. The most common reason given by community pharmacists for poor uptake of t-MURs was failure of the patient to attend, although this was often contradicted by patients who stated that their community pharmacist did not arrange a t-MUR.

Participants recruited to the study had uncontrolled asthma at baseline, with a median (IQ) asthma control questionnaire (ACQ) score of 3.00 (2.14, 3.57) across both groups, despite high doses of inhaled corticosteroid (ICS) (median (IQ) daily equivalent beclometasone-CFC dose of 1600 (800, 2000) micrograms). In the 12 months prior to the study, participants had required a mean (SD) of 4.8 (3.22) emergency courses of oral corticosteroids per person and a median of 1 hospital admission or accident and emergency department visit per person.

1.5.1 Number of interventions

At the initial consultation, participants randomised to the PI group received significantly more interventions in total than those in the UC group (total 79 vs. 34 respectively, $p<0.001$). These interventions addressed: medication-related issues (54 vs. 18); allergy tests and asthma investigations (5 vs. 1); the management of associated medical conditions (6 vs. 4); and education or advice (14 vs. 11). Possession rates of asthma action plans were similar in the two groups and increased following the baseline consultation: from 61.5% to 83.3% of participants in the PI group; and from 57.7 to 73.9% in the UC group.

1.5.2 Asthma control

The effect of pharmaceutical care in the PI group was found to be non-inferior to medical management in the UC group. At six months, the median (IQ) ACQ score had reduced (improved) from 2.86 (2.25, 3.25) and 3.00 (1.96, 3.71) in the PI and UC groups respectively to 2.57 (1.75, 3.67) and 2.29 (1.50, 3.50). Similarly, there was no difference between the two groups in the proportion of participants who had controlled asthma (defined as an ACQ <1.0 (Juniper et al., 2006)) at either baseline or follow-up. There was no significant difference between the two groups in the proportion of patient's whose asthma control improved, nor in the proportion of patients who achieved a clinically significant improvement in ACQ score (reduction of at least 0.5 units).

Participants in both groups achieved reductions in exhaled nitric oxide, and required fewer corticosteroid rescue courses and used fewer doses of short-acting $beta_2$-agonist reliever inhaler each week at follow up compared to baseline, however there was no significant difference between the two treatment arms at either baseline or follow-up.

1.5.3 Quality of life

The effect of pharmaceutical care in the PI group on asthma quality of life, using Juniper's standardised asthma quality of life questionnaire (AQLQ(S)) was found to be non-inferior to medical management in the UC group. Participants were very limited or had moderate limitation in their quality of life throughout the study; at baseline, the median (IQ) AQLQ(S) score was 4.11 (3.38, 5.21) and

3.77 (2.87, 5.30) in the PI and UC groups respectively, and at follow-up was 4.12 (3.55, 5.49) and 4.22 (2.97, 5.66) respectively. There was no significant difference between the two groups in the proportion of patient's whose quality of life improved, nor in the proportion of patients who achieved a clinically significant improvement in AQLQ(S) score (increase of at least 0.5 units).

1.5.4 Inhaler technique

Most patients had received previous inhaler technique training, although less than half of the patients had received training from healthcare professionals in primary care.

There was wide variation in the type of inhaler device prescribed, although the most frequent were pMDI (67.3%), Turbohaler (61.5%) and Accuhaler (26.9%). The majority of patients (n=34) were prescribed at least two different inhaler devices.

Errors in inhaler technique were common, with fewer than half of patients in both the PI and UC groups having optimal inhaler technique (no errors using inhaler device) using pMDI and Turbohaler devices at baseline. More patients had optimal inhaler technique using Accuhaler devices than with Turbohaler or pMDI devices (58.8% vs. 46.9% and 17.6%, respectively). Significantly more patients in the PI group compared to the UC group were assessed to have an unsatisfactory technique (at least one critical error that would significantly affect the delivered dose) using their pMDI and Turbohaler inhalers at baseline (pMDI: 17/17 vs. 10/17; Chi-Square 8.815, p=0.012; Turbohaler: 12/17 vs. 3/15; Chi-Square 8.977, p=0.011).

After education, the proportion of patients in the PI group who had optimal inhaler technique after education increased from 0% to 70.6% for pMDI, 58.3% to 92.3% for Accuhaler, and from 29.4% to 88.2% for Turbohaler. Similarly in the UC group, the proportion of patients who had *optimal* inhaler technique after education increased from 35.3% to 82.4% for pMDI, 60.0% to 100.0% for Accuhaler, and from 66.7% to 80.0% for Turbohaler.

Despite education at baseline, the proportion of patients with optimal inhaler technique was not maintained in all patients. For the six patients in the PI group who had a t-MUR at 2-months, 0% and 25% still had optimal inhaler technique with pMDI and Turbohaler devices. At six months, optimal inhaler technique was found for 6.3%, 75% and 71.4% of patients using pMDI, Accuhaler and Turbohaler devices respectively, and was not significantly different between the two intervention groups.

1.5.5 Adherence

Poor adherence was admitted by four patients in the PI group and by none in the UC group. However retrospective analysis of prescription data for the 40 participants where data were available for a six-month period prior to randomisation, median (IQ) adherence rate to ICS (defined as the percentage of prescribed doses issued compared to expected prescribed number of doses required over a six-month period) was 75.3% (35.7, 98.5). More than half of patients (57.5%) had adherence rates less than 80% and more than a third (35%) had adherence rates less than 50%. 17.5% of participants had adherence rates exceeding 100%, of whom 6 (15%) had adherence rates exceeding 120%.

At six months, a significantly greater proportion of patients in the PI group were adherent to ICS (defined as an adherence rate of 80-120%) than in the UC group (10/20 vs. 3/21, p=0.020). Good or improved adherence was not associated with improvements in asthma outcomes.

1.6 Discussion

This study recruited patients with difficult asthma, who had experienced prolonged periods of poor asthma control, frequent courses of oral corticosteroid rescue course and high use of SABA inhalers. Both intervention groups were successful in stabilising asthma control over the course of the study as there was no significant change in asthma outcome measures, and the provision of pharmaceutical care from hospital-based advanced clinical pharmacists was non-inferior to usual medical care for all asthma control measures.

Since uptake of t-MUR was poor, it is likely that the greatest impact to patients in the PI group was achieved with the baseline intervention from the hospital advanced clinical pharmacist. There is insufficient data from this study to determine whether t-MUR may achieve added benefits to patients with difficult asthma. However since inhaler technique had deteriorated by 2-months in the six patients who had received a t-MUR in the PI group, this may indicate that patients with difficult asthma require early follow-up after initial consultations to support and reinforce education and training.

The fact that fewer than half of participants had received inhaler technique in primary care may suggest that many healthcare professionals may not have sufficient knowledge about the importance of optimising inhaler technique or how to use inhaler devices.

The poor rates of adherence observed in this study are typical of populations of patients with difficult asthma. The failure to identify poor adherence in the baseline consultation suggests that asking about adherence is a poor strategy, and should be supported using prescription data.

1.7 Conclusions

Advanced clinical pharmacists who have a specialist interest in respiratory medicine have the knowledge and skills to manage difficult asthma in outpatient clinic settings. Complex pharmacist interventions incorporating asthma monitoring, inhaler technique training, medicines optimisation and adherence counselling, education, asthma action plan provision, and healthy living advice are useful in stabilising difficult asthma and preventing exacerbations. Further research should focus on how initial consultations can be supported in community settings to prevent loss of knowledge and deteriorating inhaler technique and adherence over time.

1.8 Recommendations

Specialist pharmacists should be incorporated into multidisciplinary teams working in secondary care difficult asthma clinics, and this should be a requirement of the NHS England service specification for severe asthma services.

Pharmacists in primary and secondary care should also seek to ensure that their knowledge and skills are kept up to date to ensure that their knowledge and skills are adequate to provide asthma services to patients with difficult asthma. These services should include asthma reviews with clinics as well as identifying and prioritising patients with difficult asthma for MURs. Pharmacist-led asthma reviews should be structured to ensure that all aspects of asthma management are covered including stop smoking advice, inhaler technique training, asthma monitoring, medicines optimisation, education and lifestyle advice.

Education for healthcare professionals should be prioritised to ensure that there is widespread competence in both using and training patients how to use inhaler devices.

1.9 Publication history

The publication history of the author is listed below to demonstrate experience and expertise as a pharmacist specialising in respiratory medicine. Publications that have resulted from the planning and feasibility testing of this research study, as well as presentations of interim data at an international conference, are highlighted in bold text.

1. Ahmed, R. Y., Capstick, T. G. D. and Watson, J. P. (2009) Outcomes and cost of MDR-TB in Leeds 1996-2009. *Thorax,* 64 (Suppl IV)**,** A11.
2. Capstick, T. (2007) What do respiratory function tests tell us? *Pharmacy in Practice,* 17 (7)**,** 233-237.
3. Capstick, T. (2008) Benefits of clinical pharmacy input to a tuberculosis clinic. *Guild of Healthcare Pharmacists / United Kingdom Clinical Pharmacists Association Conference* Poster No. 34.
4. Capstick, T. (2010) *Drugs in bronchoscopy. BTS Bronchoscopy eLearning Module.* London: British Thoracic Society. Available from: http://learninghub.brit-thoracic.org.uk/?bts=download&param=3&param2=134
5. Capstick, T. (2013a) Combination anti-tuberculosis therapies. *Hospital Infectious Diseases Europe***,** 38-41.

6. Capstick, T. (2014) Pneumonia: CAP, HAP and other types. *Pharmaceutical Journal,* 292**,** 54-57.
7. Capstick, T. and Alldred, A. (2007) Gout and Hyperuricaemia. In: Walker, R. and Whittlesea, C. (Eds.) *Clinical Pharmacy and Therapeutics.* 4th ed. Edinburgh: Churchill Livingstone, pp. 367-385.
8. Capstick, T. and Henry, M. T. (2005) Efficacy of thrombolytic agents in the treatment of pulmonary embolism. *Eur Respir J,* 26 (5)**,** 864-74.
9. Capstick, T. and Vigar, A. (2013a) Asthma. In: Dodds, L. J. (Ed.) *Drugs in use.* London: The Pharmaceutical Press, pp. 212-234.
10. Capstick, T. G. D. (2009) Chronic Disease Management. *Pharmacy Magazine*.
11. Capstick, T. G. D. (2011) Lower Respiratory Tract Infections. *The Pharmacist,* 12**,** 119-123.
12. Capstick, T. G. D. (2013b) Tuberculosis: Clinical features and diagnosis. *Clinical Pharmacist,* 5**,** 161-6.
13. Capstick, T. G. D. (2014) *Tuberculosis (TB): 10 ways to make a difference (e-learning).* Centre for Pharmacy Postgraduate Education. Available from: http://www.cppe.ac.uk/learning/Details.asp?TemplateID=tuberculos-E-01&Format=E&ID=47&EventID=43418
14. **Capstick, T. G. D. and Clifton, I. J. (2012) Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. *Expert Rev Respir Med,* 6 (1), 91-103.**
15. Capstick, T. G. D. and Khachi, H. (2013) New COPD options. *Pharmacy Magazine,* 19**,** 14.
16. Capstick, T. G. D. and Sanderson, R. (2011) Management of chronic obstructive pulmonary disease. *Hospital Pharmacy Europe,* 56**,** 55-58.
17. Capstick, T. G. D. and Vigar, A. (2013b) Roflumilast in severe COPD. *Hospital Pharmacy Europe,* 67**,** 53-55.
18. **Capstick, T. G. D., Clifton, I. J., Morgan, J. and Blenkinsopp, A. (2012) Medicines Use Reviews: an unmet need in difficult asthma. *Clinical Pharmacist,* Suppl 3, S43-S44.**
19. Capstick, T. G. D., Laycock, D. and Lipman, M. C. I. (2009) Treatment interruptions and inconsistent supply of anti-tuberculosis drugs in the United Kingdom. *Thorax,* 64 (Suppl IV)**,** A120.

20. Capstick, T. G., Laycock, D. and Lipman, M. C. (2011) Treatment interruptions and inconsistent supply of anti-tuberculosis drugs in the United Kingdom. *Int J Tuberc Lung Dis,* 15 (6)**,** 754-60.

21. Capstick, T., Clifton, I., Morgan, J., Silcock, J. and Blenkinsopp, A. (2013) Inhaler technique: An unmet need in patients with difficult asthma? *European Respiratory Journal,* 42 (Suppl 57), P700.

22. Denman, S. and Capstick, T. (2013) Web-based guidance for nebulised therapies. *Hospital Pharmacy Europe,* 69**,** 40-2.

23. Gill, A. L., Leong, S. A. and Capstick, T. G. D. (2014) Liver injury in treatment of latent tuberculosis infection - is the age cut-off for treatment justified? . *European Respiratory Society Congress***,** Poster P1900.

24. Gothard, A., Millington, K. and Capstick, T. G. D. (2013) Tuberculosis: management. Clinical Pharmacist 2013;5:167-70. *Clinical Pharmacist,* 5**,** 167-170.

25. Hau, T. Y. and Capstick, T. G. D. (2010) Audit of antituberculosis drugs toxicity monitoring - adherence to local Trust guidelines. *Clinical Pharmacist,* Suppl 3**,** S36.

26. Hodgekiss, C., Slough, J., Capstick, T., Peckham, D. and Clifton, I. (2013) Safety and efficacy of 7% hypertonic saline in patients with bronchiectasis. *European Respiratory Journal,* 42 (Suppl 57)**,** P745.

27. Huntington, S. and Capstick, T. G. D. (2012) Joint working sees development of web-based nebuliser guidance. *Clinical Pharmacist,* 4**,** 174-5.

28. Keal, J., Capstick, T., Ricketts, W., Whitehead, N. and Kon, O. (2013) Multi-drug resistant tuberculosis: The first UK guideline for treatment monitoring. *Thorax,* 68 (Suppl 3)**,** A119.

29. Lees, C. A. L. and Capstick, T. G. D. (2010) The role of the pharmacy technician in training inhaler technique for patients with chronic obstructive pulmonary disease. *Clinical Pharmacist,* Suppl 3**,** S37.

30. McLoughlin, H., Hart-Thomas, A., Slough, J. and Capstick, T. (2008) Use of a protocol to select patients for omalizumab treatment. *Eur Respir J,* (Suppl)**,** 345s-346s.

31. Potter, J. L., Capstick, T., Ricketts, W. M., Whitehead, N. and Kon, O. M. (2014a) *TB Drug Monographs: A UK based resource to support the monitoring and safe use of anti-tuberculosis drugs and second line*

treatment of multidrug-resistant tuberculosis. Available from: http://www.tbdrugmonographs.co.uk (Accessed 27.10.14).

32. Potter, J. L., Capstick, T., Ricketts, W. M., Whitehead, N. and Kon, O. M. (2014b) A UK-based resource to support the monitoring and safe use of anti-TB drugs and second-line treatment of multidrug-resistant TB. *Thorax***,** Published Online First: 13 June 2014. doi:10.1136/thoraxjnl-2014-205278.
33. Thomson, D. and Capstick, T. (2004) How a risk management programme can ensure safety in thalidomide use. *Pharmaceutical Journal,* 272 (190)**,** 190-191.
34. Thorp, H. and Capstick, T. (2009) Asthma. In: Dodds, L. J. (Ed.) *Drugs in use.* London: The Pharmaceutical Press.
35. Vigar, A. and Capstick, T. G. D. (2012) An audit of missed doses during inpatient admissions on respiratory wards. *Clinical Pharmacist,* Suppl 3**,** S42-S43.

2 Introduction

2.1 Asthma

2.1.1 The impact of asthma on patients and healthcare systems

Despite the availability of evidence-based guidelines and effective drugs to manage asthma, care in the UK remains suboptimal with high rates of hospital admissions (40,243 in 2011-12) and asthma deaths that remain higher in the UK than much of Europe (Royal College of Physicians, 2014), which contribute to estimated costs for around £1billion per year (Asthma UK, Undated).

The Royal College of Physicians have recently published a report of a national investigation into asthma deaths in the UK between February 2012 and January 2013 and found a significant number of areas where asthma care could have been improved (Royal College of Physicians, 2014). This study identified 3,544 people who had died and had 'asthma' documented anywhere on the death certificate. After excluding cases where no further information was available, or where asthma was unlikely be the cause of death, a total of 276 cases were reviewed by the confidential enquiry multidisciplinary panel and 195 confirmed as deaths due to asthma. The enquiry reported deficiencies in the management of asthma; 43% had not had an asthma review in the past 12 months, 57% had not been under specialist care, only 23% had an asthma action plan, 80% had sub-optimal use of preventer inhalers and 39% had been issued at least 12 short-acting reliever inhalers in the year before they died. These data clearly demonstrate that there is an unmet need in managing asthma in the UK, which could be achieved through an expanded role of clinical pharmacists. Indeed, the authors identified that pharmacists can play a key role in asthma management by identifying patients who may underuse preventer inhalers or overuse reliever inhalers, assessing inhaler technique, and providing self-management education including developing personalised asthma action plans.

Whilst previous pharmacist interventional studies have reported benefits to patients with asthma when provided with asthma education, asthma action plans, inhaler technique training, and behaviour modification (see **Chapter 3.3.1**), there remain a number of gaps in the evidence base. The majority of current research has focused on the management of asthma in community settings where most asthma patients, particularly those with mild to moderate

asthma symptoms, are routinely managed. Therefore there is minimal research examining whether pharmacists have the expertise to manage the minority of patients with severe asthma symptoms.

2.1.2 Definitions and pharmacological therapies

Asthma is a condition characterised by variable expiratory airflow obstruction resulting from chronic airway inflammation producing characteristic symptoms of wheeze, breathlessness, chest tightness and cough that vary over time and in intensity (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014).

There are an estimated 5.4 million people in the UK who are receiving treatment for asthma (National Institute for Health and Care Excellence, 2013), for which there are clear evidence-based stepwise guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). In brief, the UK guidelines advise the use of inhaled short-acting beta$_2$-agonist (SABA) inhalers for adults with mild asthma at Step 1, adding in a low dose inhaled corticosteroid (ICS) at Step 2 if uncontrolled. If still uncontrolled, treatment at Step 3 adds a long-acting beta$_2$-agonist (LABA) as a third drug and the ICS dose is then increased if necessary, up to an equivalent daily dose of 800 micrograms of beclometasone-CFC, or if the LABA is not effective a trial of an alternative such as a leukotriene receptor antagonist (LKTa) or theophylline should be attempted. If asthma is still uncontrolled in adults, Step 4 treatment requires high doses of ICS (increasing from an equivalent daily dose of 800 micrograms, up to 2000 micrograms of beclometasone-CFC) and two additional controller medicines used (e.g. LABA, LKTa or theophylline), whilst regular oral corticosteroid (OCS) should be reserved for Step 5 use only.

The majority of adults with asthma can be successfully treated with low to moderate ICS doses at Steps 1 to 3 of the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guidelines. This is because ICS have a dose-response effect in asthma, and almost 90% of the full therapeutic effect is achieved at approximate equivalent daily doses of 400 to 500 micrograms of beclometasone-CFC (Holt et al., 2001, Masoli et al., 2004). It is estimated that approximately 13.8% of patients in the UK are treated at

Steps 4 and 5 of the BTS/SIGN Asthma guidelines, and about half of these are thought to be inadequately controlled by maximal inhaled and oral therapies (Hoskins et al., 2000). These patients are labelled as having ‘difficult asthma’, which is defined as persistent symptoms and/or frequent exacerbations despite treatment at step 4 or step 5 BTS/SIGN Asthma guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014).

Throughout this thesis, patients will be described as having difficult asthma, using the definition described in the BTS/SIGN asthma guidelines, rather than using similar alternative definitions or terminologies of severe asthma used by the European and American Respiratory Societies (Chung et al., 2014), or the World Health Organisation (WHO) (Bousquet et al., 2010). This is because most UK practitioners use the BTS/SIGN asthma guideline definition, and so a study that recruited patients who meet these criteria would allow the results to be interpreted within the context of UK practice.

The prevalence of difficult asthma has been estimated at 5-10% of the total asthma population, although there is some uncertainty with this figure due to variations in definitions of difficult or severe asthma used (Chung et al., 2014). The appropriate and effective management of difficult asthma accounts for a relatively large proportion of resource expenditure in asthma because they are treated with more medicines at higher doses and often remain uncontrolled compared to adults with mild to moderate severity asthma (O'Neill et al., 2014). Furthermore the management of asthma exacerbations incurs greater costs than maintenance management of asthma, and tends to be more expensive in adults with difficult asthma (Hoskins et al., 2000, Chung et al., 2014). One five-year pharmacoeconomic study found that the mean cost of treating patients in primary care at step 4 and 5 of the BTS/SIGN asthma guidelines (i.e. the steps at which patients with difficult asthma are treated) was 3.5 to 16 times higher than the mean annual cost of managing patients at steps 1 to 3 (Das Gupta and Guest, 2003). The main costs incurred were associated with General Practitioner (GP) consultations and prescription medicines, where there may be opportunities for pharmacists to help improve asthma management.

Although the severity of asthma may vary between patients, the aim of treatment at Steps 1 to 5 remains the same; specifically to achieve and maintain asthma control and normal activity levels, and minimising the future risk of exacerbations, fixed airflow limitations and adverse effects (Global Initiative for Asthma, 2014, British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). This was found to be achievable in the majority of patients in the Gaining Optimal Asthma controL (GOAL) study, including those who were uncontrolled on low to moderate ICS doses at baseline (Bateman et al., 2004, Bateman et al., 2008, Woodcock et al., 2007). This therefore demonstrates that achieving asthma control should be an appropriate goal and is achievable for most asthma patients.

However, difficult asthma is a complex multifactorial condition and patients are commonly referred to specialist hospital services led by consultant physicians in order to improve patient outcomes such as exacerbation frequency, mortality, lung function and quality of life (NHS England, 2013). Due to the complexity of difficult asthma, the goal of difficult asthma management is frequently to stabilise the condition and maintain as high a level of asthma control and quality of life as possible rather than achieving total asthma control, which may not be achievable in all patients.

2.1.3 Non-pharmacological interventions in asthma

Asthma is a complex multifactorial condition and it has been shown that brief or limited interventions may not to be as effective as more complex multi-faceted interventions targeting different aspects of asthma management. In one systematic review, isolated limited asthma education, such as aspects of the disease process, its causes and its treatment, did not significantly affect health outcomes in terms of hospitalisations, doctor visits or medication use; however it did improve patient's perceptions of their symptoms (Gibson et al., 2002b). A second systematic review of patient education combined with providing self-management education and action plans, combined with regular medical review demonstrated significant improvements in hospitalisations, emergency room visits, indirect costs and quality of life (Gibson et al., 2002a).

Current national and international asthma guidelines used in the UK recommend that the management of asthma requires a mixture of pharmacological and non-pharmacological therapies, as well as advocating patient education and self-management strategies (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014). Non-pharmacological management strategies include allergen and trigger avoidance, weight reduction and smoking cessation and have been demonstrated in some cases to have significant benefits on asthma control (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014).

2.1.4 Pharmacy services for asthma patients

There is a potential role for pharmacists to perform asthma reviews, either in hospital clinics or as part of Medicines Use Reviews (MURs) and the New Medicines Service, in order to optimise asthma medicines and improve medicine use, as well as to identify and address non-adherence. Patients with difficult asthma should be targeted since they commonly experience persistent breakthrough asthma symptoms such as wheeze, breathlessness, chest tightness and cough, night-time waking and limitation of daily activities. They are also at risk of frequent severe exacerbations requiring rescue courses of OCS and associated GP attendance, Accident and Emergency (A&E) visits and hospital admissions and adverse reactions to prescribed medication, as well as being at an increased risk of death (Heaney et al., 2003, Barnes and Woolcock, 1998, Wener and Bel, 2013, Chung et al., 2014, Bousquet et al., 2010, Royal College of Physicians, 2014).

In recent years, many pharmacists have developed their skills to provide asthma management services to patients with asthma in both hospital and community settings (Benavides et al., 2009). The ability of pharmacists to teach self management skills, correct inhaler technique and identify non-adherence in asthma patients is recognised in asthma management guidelines as effective for improving asthma control (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014). In particular, pharmacists have been shown to produce significant improvements in asthma outcomes in community pharmacy settings (Armour et al., 2007, Saini

et al., 2008), and more recently pharmacists have been performing asthma reviews in GP practices (Khachi and Karikari, 2013).

The role of pharmacists working in secondary care difficult asthma clinics is less well studied despite a number of UK pharmacists working alongside consultant physicians, specialist nurses and physiotherapists in these settings. Published studies in hospital settings have generally reported the effects of asthma management provided by physicians and pharmacists working in collaboration. One such study reported the role of pharmacists supporting the interventions made by physicians in US hospital outpatient clinics rather than working independently to provide asthma reviews. The pharmacist role was to provide education on self-management and was reported to produce similar improvements in asthma quality of life and exacerbations to usual physician care alone over a 45 day period (Knoell et al., 1998). This demonstrated that pharmaceutical care could potentially assist usual medical management of asthma in hospital outpatient clinics. However limitations on the study design, such as selective patient recruitment and lack of randomised allocation, prevent firm conclusions to be made on the potential added benefit of asthma management provided by specialist hospital pharmacists on overall outcomes. This lack of research studies may explain why the first draft of the National Health Service (NHS) England service specification for severe asthma services fails to specify that a specialist pharmacist should be part of the severe asthma multidisciplinary team (NHS England, 2013).

In primary care, UK Community Pharmacists, accredited by a Higher Education Institution, are funded to provide an MUR service to review the use of medicines for long-term conditions in individual patients. The underlying purpose of MUR services is, with the patient's agreement, to improve the patient's knowledge and use of drugs by (i) establishing the patient's actual use, understanding and experience of taking drugs; (ii) identifying, discussing and assisting in the resolution of poor or ineffective use of drugs by the patient; (iii) identifying side effects and drug interactions that may affect the patient's compliance with instructions given to them by a health care professional for the taking of drugs; and (iv) improving clinical and cost effectiveness of drugs prescribed to patients, thereby reducing the wastage of such drugs (Department of Health, 2013).

At the time of this study, the terms of service allowed for each patient to have a maximum of one MUR in a 12-month period (unless there were sufficient changes in a patient's circumstances to justify a further MUR) and at least 50% of MURs had to be targeted MURs (t-MUR), specifically for patients who are: (i) prescribed a high risk medicine (non-steroidal anti-inflammatory drug, anticoagulants, antiplatelets or diuretics); (ii) recently discharged from hospital with changes to their regular medicines; or (iii) prescribed a respiratory drug (bronchodilator, corticosteroid, cromoglicate, LKTa or phosphodiesterase type-4 inhibitor). Community pharmacists use a standard MUR form to collect data on each consultation, and a copy is provided for the patient and their GP with a list of interventions and recommendations made. Pharmacists are required to record all issues identified and interventions made including healthy living advice, non-adherence, problems taking medicines or using devices, education provided, adverse drug reactions, and reasons for expected improvement in adherence (Pharmaceutical Services Negotiating Committee, 2013). The MUR service in Leeds is well established, with 93.7% of the 174 community pharmacies in Leeds providing MUR services in 2012-13, and a total of 46,222 MURs undertaken (Prescribing and Primary Care team, 2013). Published data does not report the number of t-MURs performed, so it is unclear whether respiratory drug t-MURs are also well established.

The role of MURs to target specific patient groups such as those with asthma is justified as reviews have reported that there is evidence that they may improve outcomes (Blenkinsopp, 2010). Two studies, which will be discussed in the literature review (**Chapter 3.3.2**), have demonstrated that existing community pharmacy services can be successfully utilised to improve asthma management (Bagole et al., 2007, The Cambridge Consortium, 2012), although there is a lack of data specifically assessing their impact specifically in patients with difficult asthma.

Although pharmacists have been identified as being competent to provide asthma services, there are no studies assessing the impact of the transition of asthma services between secondary and primary care pharmacists. Patients with difficult asthma should receive regular follow-up reviews (British Thoracic

Society Standards of Care Committee, 2008), and since these patients need to collect regular prescriptions for a number of asthma medicines, there are regular opportunities for community pharmacists to provide support for asthma management.

There is an absence of published research investigating the effects of community pharmacists performing follow-up reviews of patients with difficult asthma, and this appears to be a real problem in clinical practice. A pilot study preceding this study demonstrated that only one third of patients attending the difficult asthma clinic had received a MUR within the past 12 months (Capstick et al., 2012). Therefore there is a need for research to investigate this opportunity for community pharmacists to provide follow-up reviews using the funded MUR service.

2.1.5 NHS Outcomes strategy for Chronic Obstructive Pulmonary Disease (COPD) and asthma

The NHS outcomes strategy for COPD and asthma require healthcare professionals to "ensure that people with asthma…are free of symptoms because of prompt and accurate diagnosis, shared decision making regarding treatment, and on-going support as they self manage their own condition and to reduce need for unscheduled health care and risk of death" (Department of Health, 2011). This is supported by the National Institute for Health and Care Excellence (NICE) quality standards for asthma, which describe the high priority areas for quality improvement in asthma care, and describe a number of areas where pharmacists should take an increasing role in asthma management (National Institute for Health and Care Excellence, 2013). NICE advise that people with difficult asthma are offered an assessment by a multidisciplinary asthma service, because they need specialist assessment to ensure an accurate diagnosis and exclude alternative causes, manage comorbidities, confirm adherence and ensure they receive the most appropriate treatment. However, as NICE do not specify which healthcare groups should form this multidisciplinary team, pharmacists may be overlooked as a key member, which may be to the detriment of patients with difficult asthma.

Pharmacists are well placed and have the appropriate training and skills to focus on a number of NICE quality standards, including provision of a written personalised action plan (statement 3), training and assessment of inhaler technique (statement 4), structured asthma reviews in the community (statement 5), and assessment of asthma control (statement 6). Since the optimum management of asthma relies heavily on using inhaler devices correctly and good adherence, which may be facilitated through good consultation skills, it is important to understand the theory underpinning these issues when designing a research study.

2.2 The effect of inhaler technique on asthma control

2.2.1 The science of inhaler technique

The use of inhaled therapy has a number of advantages over systemic therapy, as it allows a smaller dose to be administered, with a faster onset of action and fewer systemic side effects (Everard, 2001, Newman, 1985). The deposition of the inhaled drug in the lung is dependent on particle size, inhalation technique and the type of inhaler device. Consequently correct inhaler technique is of critical importance, since errors in inhaler technique are associated with suboptimal delivery of the drug into the lungs and may also potentially increase the risk of adverse effects, particularly with ICS (Capstick and Clifton, 2012). To understand the importance of performing the correct steps in using inhaler devices in asthma, it is essential to understand the science behind inhaler technique.

The lung deposition of inhaled drugs is dependent on three different mechanisms: inertial impaction, sedimentation and diffusion. However, as aerosol therapies require particles 1–10 μm in size in order to target central and peripheral airways, only inertial impaction and gravitational sedimentation are important. The third mechanism, Brownian motion/diffusion, is only relevant in aerosols of less than 1 μm in diameter (Bell, 2008, Newman, 1985), and therefore is unlikely to be of consequence for inhaled drugs.

Inertial impaction occurs with large or high velocity particles in either the oropharynx or at bifurcations of main branches of the bronchial tree, particularly

in the large central airways, where they are unable to follow the airstream when it changes direction, thus impacting on the airway wall (Bell, 2008, Newman, 1985). Gravitational sedimentation occurs for smaller particles that are able to follow the airstream and penetrate the more peripheral bronchioles and alveoli. Here the airstream flows more slowly, allowing the particles to settle on to the airway surfaces either during the course of slow steady breathing or during breath-holding (Bell, 2008, Newman, 1985). Breath-holding is important for smaller particle sizes owing to the increased chance of exhalation of the drug, because they can remain airborne for a considerable time (Usmani et al., 2005), with more than half of 1.5 μm particles remaining airborne for over 5 minutes (Biddiscombe et al., 2003).

The total lung deposition of an inhaled drug from a dry powder inhaler (DPI) is strongly affected by the turbulent energy generated in the inhaler device during inhalation, which causes the powder formulation to de-aggregate and produce an emitted dose with a particle size distribution that will penetrate the peripheral airways (Azouz and Chrystyn, 2012). This turbulent energy is generated through a combination of inspiratory flow and the resistance of the inhaler device, such that DPIs require a fast and deep inhalation to create the pressure drop required to ‘suck up’ the drug in the inhaler device (Bell, 2008, Chrystyn, 2003, Haughney et al., 2010). Failure to achieve this high internal force increases the likelihood of the dose impacting in the mouth and throat, due to generation of large drug particles with a high inertia.

By contrast, aerosol inhalers, such as the pressurised Metered Dose Inhaler (pMDI), require a slow and deep inhalation, with an inspiratory flow rate (IFR) of less than 60 L/min. This is because aerosol inhalers generate their own aerosol, and so a slower inhalation rate is required to ensure that the drug deposits in the peripheral airways, since a fast inhalation will increase the velocity of the drug particles, thus increasing inertial impaction in the oropharynx (Al-Showair et al., 2007, Haughney et al., 2010). Alternatively, the use of extra-fine particles in a pMDI device results in increased lung deposition at higher IFRs, since inertial impaction is a function of the velocity and size of drug particles (Usmani et al., 2005).

IFR measurements through inhaler devices is of importance, since a significant proportion of patients with asthma have been shown to have an inspiratory flow too high for an pMDI, which could potentially reduce the clinical effectiveness of inhaled drugs (Al-Showair et al., 2007). Similarly, slow IFRs through DPIs (such as the Accuhaler, Easyhaler and Turbohaler) have been shown to reduce lung deposition of inhaled drugs (Borgström et al., 1994, Palander et al., 2000), which again adversely affect clinical effectiveness.

The In-Check DIAL® inspiratory flow meter (Clement Clarke Ltd, UK) can be used to ensure that patients can inhale through their inhaler device at the clinically effective IFR. The device mimics the internal resistance of a range of inhaler devices (Accuhaler, Easi-Breathe, HandiHaler, pMDI and Turbohaler devices), allowing the measurement of IFR through these devices (Chrystyn, 2003, Nsour et al., 2001), and can be used as part of inhaler technique assessments. There are alternative training aids available to assist inhaler technique training with specific inhaler devices such as the Turbohaler Trainer (AstraZeneca, Sweden), the Accuhaler training Device (Vitalograph, Ennis, Ireland), the 2-Tone Trainer® (Canday Medical Ltd, UK), and the Flo-Tone Trainer (Clement Clarke International Ltd, UK), which can be used to train patients to inhale at the correct IFR when using a Turbohaler, Accuhaler or pMDI.

2.2.2 Patients' ability to use inhaler devices

The ability to use inhaler devices correctly is crucial to the management of asthma, but despite this, many patients make multiple and/or serious errors using their inhaler devices. This is of concern, since poor inhaler technique is known to result in significant reductions in the effective dose reaching the lungs (Newman et al., 1995, Newman, 1985), which would affect the clinical effectiveness of the inhaled drug. In a relatively old systematic review, the optimum inhaler technique (where no errors are made), was observed in 23-43% for pMDI, 53-59% for DPIs and 55-57% for pMDI + spacer (Brocklebank et al., 2001). However this systematic review included patients with different respiratory conditions across all age groups, and included within the meta-analysis a wide variety of DPIs (several no-longer available in the UK) including data from Cyclohalers, Diskhalers, Rotahalers, Spinhalers and Turbohalers,

making an unjustifiable assumption that inhaler technique is similar for all DPIs. This is clearly not the case, as there is diverse range of different DPI devices with different methods for orientation and priming prior to inhalation, and with different internal resistances requiring different inspiratory efforts. In one real-life study of 3,811 inhaler technique assessments performed on people with asthma or COPD in 575 GP practices in France, at least one error was made by 76% of patients using a pMDI, 54% using a Turbohaler and 49% using an Accuhaler (Molimard et al., 2003). Furthermore, at least one critical error (defined as an error liable to substantially affect dose delivery to the lung) was observed in 28% of patients using a pMDI, 32% using a Turbohaler and 11% using an Accuhaler, clearly demonstrating that some inhaler devices may be easier to use than others.

Despite increasing recognition of the importance of good inhaler technique, studies in GP practices, hospital outpatient clinics and community pharmacies continue to report high prevalence of poor inhaler technique in asthma patients. However the rate of good inhaler technique continues to be highly variable across studies, even for devices that are very commonly prescribed. In one study assessing the inhaler technique of 4,078 adult asthmatics using pMDI devices in GP practices, 71% were considered to be poor users and 33% were poor coordinators, based on a checklist assessment (Giraud and Roche, 2002). However two more recent studies, again based in GP practices, used the Vitalograph Aerosol Inhalation Monitor to assess pMDI inhaler technique; in one study of 1,291 adult asthma patients 85.6% failed to demonstrate optimum inhaler technique at the first attempt (Hardwell et al., 2011), but in a second study in 2,480 adult asthma patients only 58% failed at the first attempt (Levy et al., 2013).

The variation in prevalence of good and poor inhaler technique reported in different studies is likely to be in part due to a chance finding, but also reflects inconsistencies in study design and inhaler technique assessments. Basheti et al, 2014, recently described concerns over the lack of a defined standard for assessing inhaler technique, in particular with regards to the number and content of inhaler checklists, which makes it difficult to compare and contrast findings from study to study, and few have been validated by supporting

evidence that improving inhaler technique results in improvements in asthma outcomes (Basheti et al., 2014). A further concern with many studies is that there is very rarely an objective measure on inspiratory flow through inhaler devices, which is known to be critical to lung deposition. The In-Check DIAL inspiratory flow meter is a useful tool that allows studies to objectively measure inspiratory flow through different inhaler devices, but is only useful for a limited range, and not for newer inhaler devices such as the Easyhaler, Ellipta, NEXThaler or Spiromax devices.

2.2.3 Effect of inhaler technique on asthma

Concerns over poor inhaler technique arise since the significant reduction in the dose delivered to the lungs has been demonstrated to adversely affect asthma control using measures such as the Asthma Control Test (ACT) (Baddar et al., 2014, Melani et al., 2011), asthma instability scores (Giraud and Roche, 2002), and Juniper's Asthma Control Questionnaire (ACQ) (Giraud et al., 2011). Poor technique has also been associated with increased $beta_2$-agonist use, nocturnal waking, exercise-induced dyspnoea, emergency room visits, and increased global perception of asthma (Giraud and Roche, 2002, Melani et al., 2011).

It is often considered that the most important errors to avoid in the process of using an inhaler device are the 'critical' or 'essential' steps, where failure to perform these steps would result in a substantial reduction in emitted dose, or even result in no dose being delivered. Examples of critical errors include failure to remove the inhaler cap, failure to prime or actuate device, and failure to inhale correctly through the device (Basheti et al., 2014, Melani et al., 2011, Molimard et al., 2003). Melani *et al* (2011) demonstrated that patients who make at least one critical error using an inhaler had significantly worse asthma control, and higher rates of OCS use and hospital admissions (Melani et al., 2011). Despite this recognition that critical errors are likely to have the most serious consequence for asthma management, no studies have examined the impact of critical errors compared to minor errors on asthma control.

2.2.4 Healthcare professionals' ability to use inhaler devices

Since poor inhaler technique has been demonstrated to have an adverse effect on asthma control, it is important that healthcare professionals are competent at

using inhaler devices and are able to teach correct inhaler technique to patients. However in one UK study across primary and secondary care, only 7% of healthcare professionals (including hospital doctors, hospital nurses, GPs, practice nurses, hospital and community pharmacy staff) were able to adequately perform the correct inhaler technique for a pMDI, including having the correct IFR. This demonstrates that poor inhaler technique is common across all healthcare professionals and not limited to one group of professionals (Baverstock et al., 2010). Similarly poor inhaler technique has been demonstrated by healthcare professionals using pMDIs in an Oman study (Baddar et al., 2001), specialist respiratory doctors and nurses, or emergency department staff using pMDIs in US studies (Interiano and Guntupalli, 1993, Jones et al., 1995), and hospital pharmacists using pMDIs, Accuhalers and Turbohalers in a Canadian study (Jackevicius and Chapman, 1999).

This consistent finding that healthcare professionals frequently have poor inhaler technique highlights their need for training to improve their knowledge and skills, in order that they can then teach patients how to use their inhalers correctly. Basheti et al, 2009, demonstrated that one 3-hour evening educational workshop on asthma and inhaler technique training was sufficient for pharmacists to learn and maintain optimal inhaler technique using Accuhaler and Turbohaler devices. In this single-blind randomised controlled trial involving 31 community pharmacists, those in the active education group demonstrated significantly better inhaler technique at 2-years than pharmacists in the control group who had not received inhaler technique training (Basheti et al., 2009).

Individual or small-group teaching methods, which incorporate practical demonstrations have consistently been demonstrated to significantly improve the inhaler technique of healthcare professionals including pharmacists (Basheti et al., 2009, Cain et al., 2001, Jackevicius and Chapman, 1999) and junior doctors (Resnick et al., 1996). This method appears to be more effective than less intensive training using written materials only (Jackevicius and Chapman, 1999), but as good as self-directed web-based training with video demonstration of correct inhaler technique (Toumas et al., 2009).

However, whilst Basheti et al demonstrated that improved technique following intensive small-group teaching could be maintained over prolonged periods (Basheti et al., 2009), this was not replicated in other studies (Jackevicius and Chapman, 1999, Resnick et al., 1996). These contrasting findings may be explained by the fact that the community pharmacists who maintained good inhaler technique were using these skills routinely in a structured interventional study designed to improve patients' inhaler technique and asthma control (Basheti et al., 2009), whilst the hospital pharmacists (Jackevicius and Chapman, 1999) and junior doctors (Resnick et al., 1996) may not have been involved with regular inhaler technique education and were not involved in an interventional study on improving patient's inhaler technique. The authors of these two latter studies concluded that one-time education for healthcare professionals on inhaler technique is unlikely to be effective in the long-term.

The implication for practice, is that any study that aims to improve patients' inhaler technique would have to ensure that the healthcare professionals or researchers performing the intervention are adequately trained, skilled and knowledgeable in the correct use of a range of inhaler devices, and may need this training reinforced if they do not regularly teach inhaler technique for prescribed inhaler devices.

2.3 Adherence and behaviour modification

Poor adherence to asthma medication has been consistently described in the medical literature and has been demonstrated to be a significant issue across all drug classes including ICS (Horne and Weinman, 2002, James et al., 1985), OCS (James et al., 1985, Glanz et al., 1984), theophyllines (James et al., 1985), inhaled SABAs and LABAs (James et al., 1985, Kinsman et al., 1980) and oral $beta_2$-agonists (James et al., 1985). Since ICS are considered to be the most-effective preventer drug for achieving asthma control (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014), it is critical that adherence to this class of drug is maintained. However a systematic literature review in asthma reported that short-term studies (with a two to 12 week duration) demonstrated that patients took the recommended doses of medication on 20% to 73% of days, underusing their ICS on 24% to 69% of

days, and overusing on 2% to 23% of days (Cochrane et al., 2000). In a five-year study, adults with asthma were reported to only adhere to their asthma prescriptions for around 30% to 60% of the time, based on prescription data. Furthermore, 25% of patients with mild to severe asthma had compliance rates estimated at 30% or less (Das Gupta and Guest, 2003).

Factors affecting adherence are complex and are described as intentional non-adherence (when the patient makes a conscious decision not to take their medication) or unintentional non-adherence (such as when the patient forgets to take their medication or is unable to use their prescribed inhaler devices) (Cochrane et al., 1999, Horne, 2006). Intentional non-adherence to ICS in asthma is particularly common and has been shown to be closely related to patients' beliefs, particularly due to doubts about the necessity for medication, concerns about the potential for adverse drug reactions, and perceived consequences and perceptions of their illness (Horne and Weinman, 2002, Horne and Weinman, 1999, Menckeberg et al., 2008).

It is important to identify poor adherence to ICS because it is known to result in poor asthma outcomes and increased mortality (Suissa and Ernst, 2001, Suissa et al., 2000). Confusingly, some studies have shown higher self-reported adherence rates in people with more severe asthma (Bolman et al., 2011, Clark et al., 2012), when it would be more logical to find that poor adherence resulted in more severe asthma symptoms. This may be explained by the fact that these two studies used self-reported measures of adherence rather than objective measures such as prescription data or dose monitoring, and so may be subject to over-reporting. On the other hand, it may be logical to anticipate that increasing severity of asthma symptoms may provide a stimulus to patients to adhere to their treatment regimen, but this should then result in improved asthma control and show an association between adherence and fewer asthma symptoms. This suggests, therefore, that the inter-relationship between asthma control and adherence are complex, and other factors may also be important.

Other factors that are associated with improved adherence in asthma include having fewer negative perceptions of ICS, habitual use of ICS (Bolman et al., 2011), and presence of an asthma action plan (Clark et al., 2012). Conversely,

factors that may be associated with poorer adherence in asthma include concerns about side effects, more negative perceptions of ICS (Sofianou et al., 2013, Park et al., 2010), impulsivity (Axelsson et al., 2009), forgetfulness and having to take inhaled medicines more than once a day (Park et al., 2010). Furthermore, cohort studies have suggested that the choice of inhaler device may also affect adherence, with one cohort study reporting improved adherence using a DPI rather than a pMDI device. This may have been due to patients' preference for DPI devices, being easier to use, or due to greater symptomatic improvement using DPIs, which tended to be an ICS/LABA combination inhaler whilst pMDIs contained ICS alone (Roy et al., 2011).

These studies suggest that adherence may be improved by education on asthma management in order to address misconceptions or to allay concerns about taking medications, as well as ensuring that the inhaler device prescribed is acceptable to the patient. A literature review focussing on the effect of interventions aiming to improve adherence is presented in **Chapter 3.3.4**.

2.3.1 How adherence to inhaled corticosteroids affects asthma control

The importance of adherence to ICS in asthma has been demonstrated in a number of studies analysing a link between adherence and asthma control.

Despite the fact that patient-reported adherence frequently over-estimates true adherence (Hyland et al., 2012, Ivanova et al., 2008), two studies have demonstrated that better patient-reported adherence shows a weak correlation with asthma control using the ACT (Wojtczak et al., 2012), a reduction in emergency room visits and improved quality of life (Takemura et al., 2010). However another failed to demonstrate an association between adherence using the Medication Adherence Report Scale (MARS) questionnaire and asthma control using ACT (Axelsson et al., 2009), although this may have been confounded by the overall sample population having a mean ACT of 21.34 indicating a sample population with well controlled asthma, and thus having less scope for improving asthma control further.

There are concerns over patient-reported measures of adherence, and this was highlighted in a cohort study that reported that whilst there was an association

between asthma exacerbations and adherence when measured with prescription records, there was not when patient self-reported adherence was used (Hyland et al., 2012). This disparity in association between asthma exacerbations and adherence measured using two different methods may be due to over-estimation of adherence when reliant on patients' memories. This is supported by the fact that studies that measured adherence using prescription record data have demonstrated significant associations with asthma control using ACT (Baddar et al., 2014), asthma quality of life using Juniper's Asthma Quality of Life Questionnaire (AQLQ) (Gamble et al., 2009), lung function using Forced Expiratory Volume in 1 second (FEV_1) and sputum eosinophil counts (Murphy et al., 2012b), and exacerbations (Williams et al., 2011). In contrast, one study did not find a significant association between adherence and asthma control using ACQ (Murphy et al., 2012b).

A concern with these studies lies in the variation of the cut-off for good or poor adherence making it hard to compare findings between studies; with a 50% adherence rate being used to analyse the impact on asthma symptoms and control in one study (Gamble et al., 2009), and 75% (Williams et al., 2011, Hyland et al., 2012), or 80% in others (Murphy et al., 2012b). However, the cut-offs used to define good or poor adherence appear to be an arbitrary value, with no large real-life studies available to adequately determine what is the lower limit for good adherence that may be associated with an optimal clinical effect.

Similarly real-life adherence in other long-term conditions is substantially lower than achieved in clinical trials, with adherence rates commonly between 33% and 50%, representing a personal and economic loss to patients, the healthcare system and society (National Institute for Health and Care Excellence, 2009). Adherence studies in other long-term conditions similarly appear to use arbitrary values to define good adherence without data to confirm that these achieve optimum clinical effects (Esposti et al., 2011, Slejko et al., 2014). This contrasts with the use of antiretrovirals in HIV (human immunodeficiency virus) infection, where adherence rates less than 95% have been demonstrated to increase the risk of treatment failure (WIlliams et al., 2012). The lack of clear information on the effect of adherence on treatment outcomes for many long-term conditions such as asthma therefore makes it difficult for healthcare professionals to

advise patients about definite adherence requirements, which would otherwise assist concordant management discussions. Other interventions are therefore required to improve adherence in asthma.

2.3.2 Measuring adherence to inhaled corticosteroids in asthma

Different methods of assessing adherence may under or over-estimate the true rate of adherence in asthma and other long-term conditions. In particular, indirect methods commonly used in asthma such as those based on clinical judgement, patient self-reporting and dose counting are often unreliable or subject to a high degree of under or over-estimation (Cochrane et al., 1999, Osterberg and Blaschke, 2005). In asthma, patient reported adherence has been demonstrated to over-estimate true adherence based on prescription collection data (Hyland et al., 2012, Ivanova et al., 2008). In one study, patient self-reported good adherence on the Morisky scale (a 4-item questionnaire) was 20.7%, but only 2.7% met the definition of good adherence (defined as ≥80% medication possession ratio) based on prescription collection data (Ivanova et al., 2008). A similar observational study reported that 32% of patients reported regular use of ICS, 14% reported regular but suboptimal use of ICS and 54% reported symptom-directed use of ICS. However prescription data demonstrated only that only 28% regularly used their ICS (Hyland et al., 2012). It should be noted, however that objective measures of adherence such as prescription refill data may produce inaccurate data since there is no guarantee that patients will use their inhalers if they get them dispensed, and refill counts from pharmacies may under-estimate adherence if patients use multiple pharmacies (Cochrane et al., 1999, Osterberg and Blaschke, 2005).

In an attempt to overcome disadvantages of indirect adherence assessments, the MARS (Horne and Weinman, 2002) was developed. This is a self-report questionnaire that utilises non-threatening questions in order to encourage patients to openly describe their medication adherence, and has been validated in a study comparing asthma patient's self-reporting to pharmacy prescribing records (Menckeberg et al., 2008). Consequently, the MARS may be a useful questionnaire to use in research and clinical practice to assess adherence.

2.3.3 Strategies to improve medication adherence

Common methods used in clinical practice to improve adherence in asthma have often focussed on simplifying treatment regimens such as through the use of combination ICS/LABA inhalers, rather than separate ICS and LABA inhalers. This is frequently justified because studies have demonstrated greater adherence to LABA inhalers than to ICS inhalers when given separately (Murphy et al., 2012b), which may be due to subjective improvements observed by patients receiving bronchodilators compared to ICS where long-term benefits may not be perceived as easily. However, there has been a significant body of research that has sought to determine whether adherence can be improved through modifying behaviours.

Cognitive-based behaviour change techniques (CBCT) are becoming increasingly recommended for use by healthcare professionals to improve adherence. A recent meta-analysis across a range of medical conditions including asthma, tuberculosis, HIV, epilepsy, diabetes and hypertension found a significant improvement in medication adherence through the use of CBCT. Such interventions included motivational interviewing, one to one counselling sessions, and brief intervention to elicit beliefs and resolve barriers (Easthall et al., 2013). Motivational interviewing was one of the most common forms of CBCT employed across the studies since it is designed to address patient's ambivalence to change, targeting intentional non-adherence, as well as reflecting on unintentional non-adherence in order to facilitate behaviour change and identify solutions to resolving non-adherence (Easthall et al., 2013).

Further evidence that supports the benefit of combinations of behaviour modification interventions is asthma is provided by a systematic review, which investigated the efficacy of different components of the Chronic Care Model (CCM) to improve adherence to ICS in asthma (Moullec et al., 2012). The CCM incorporates interventions such as self-management, decision support (such as evidence-based guidelines and integrating specialist services), delivery system design (such as the use of multidisciplinary teams, including pharmacists) and clinical information system (such as clinical registries). The systematic review incorporated 18 studies, all but one of which was conducted in patients with moderate to severe asthma, and all included a self-management component,

including education about the condition as well as prevention and treatment strategies, behavioural support including monitoring and incorporating tools to modify behaviours, and motivational interviewing. Of the 13 studies that incorporated just one CCM component (12 taught self-management skills and one used decision support), a significant improvement in adherence was found, with a pooled effect size of 0.29 (95% CI 0.16-0.42), such that mean adherence in the intervention group was 0.29 of a standard deviation above the control group mean. However when two or four CCM components were used, the pooled effect size was greater at 0.53 (95% CI 0.40-0.66) and 0.83 (95% CI 0.69-0.98) respectively (Moullec et al., 2012).

This study therefore suggests that whilst a consultation that incorporates CBCT interventions such as self-management strategies is important, it still needs to be incorporated with other interventions. Such consultation methods have been employed successfully in a Belfast adherence study, which used an intervention based on a Compliance Therapy Model encompassing the Transtheoretical Model of Change, Motivational Interviewing and Cognitive Behavioural Therapy principles (Gamble et al., 2011). This intervention resulted in a significant improvement in adherence to ICS.

Studies that incorporated combinations of individualised interventions seeking to alter behaviours have demonstrated significant improvements in asthma symptoms as a direct result of changes in asthma behaviours (Bailey et al., 1990, Put et al., 2003, van Es et al., 2001). In one study, an intensive programme of six 1-hour sessions was used to provide psycho-education about each patient's illness perceptions and what causes their symptoms, behavioural techniques such as self-monitoring and the control and avoidance of asthma triggers, and cognitive techniques designed to address erroneous views about asthma and its treatment (Put et al., 2003). At three months, this intervention was associated with a significant improvement in quality of life as measured using the AQLQ (increase of 0.9 vs. -0.1, $p<0.0001$), lung function as measured using peak expiratory flow and adherence after completion of the programme and after three months follow-up. This study therefore demonstrates the value of consultation styles focusing on behaviour changes in asthma as an intervention that can improve asthma symptoms.

2.4 Summary

There may be potential for improvement of the care and health of patients with difficult asthma through the better use of medicines and greater input from pharmacists, but more research is needed. In particular, research is needed to determine whether a co-ordinated approach comprising complex interventions from hospital specialist pharmacists and community pharmacists improves asthma control or other asthma outcome measures. A number of areas have been highlighted in this chapter that demonstrate issues affecting medicines use that may influence asthma control. Before commencing a research study, it is important to understand previously published literature in order to identify aspects of asthma management where the evidence base is lacking in order to develop a research study to address these gaps.

The research study presented in this thesis is the first to investigate the effects of a redesigned pharmaceutical pathway across the primary and secondary care interface in patients with difficult asthma. It is also the first to compare pharmaceutical management of asthma to usual medical care, since previous studies have focussed on comparisons of enhanced pharmaceutical management to usual pharmacist management (Armour et al., 2007, Barbanel et al., 2003, Charrois et al., 2006, Cordina et al., 2001, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Mehuys et al., 2008, Petkova, 2008, Saini et al., 2008).

The research question being examined is whether a co-ordinated management strategy between a hospital Advanced Clinical Pharmacist specialising in respiratory medicine and community pharmacists can improve asthma control in patients with difficult asthma.

2.5 Aim

To determine the effects of a co-ordinated management strategy between primary and specialist secondary care pharmacists on asthma control and quality of life in patients with difficult asthma.

2.6 Objectives

This primary objective of this study is to measure the impact on asthma control from the management of difficult asthma by a hospital advanced clinical pharmacist and community pharmacist.

Secondary objectives are to determine the impact of the intervention on quality of life, exacerbations, lung function, inhaler technique and adherence.

The results of this study will be used to make recommendations for the future delivery of services provided by pharmacists for patients with difficult asthma.

3 Literature Review

3.1 Introduction

During the planning of a research study on how pharmacists may impact on the management of patients with difficult asthma, it is important to critically analyse published literature in order to understand how the current evidence-base influences potential study aims and objectives. A new research study should build on existing research as well as seeking to investigate areas of practice where there are currently gaps in the literature and identify areas where research is lacking. This literature review will critically analyse research investigating the different aspects of how pharmacists may intervene in the management of asthma, concentrating on the role of complex interventions, inhaler technique, and adherence on asthma control.

3.2 Literature review methods

The methods used in this literature review are based on the those recommended by the Cochrane Collaboration for performing systematic reviews (Higgins and Green, 2011). Cochrane recommend that Cochrane review groups include a trials search co-ordinator to assist with the search for studies for inclusion in reviews, by designing search strategies and running these in the selected bibliographic databases. Where trials search co-ordinators are not available, Cochrane recommend that guidance is sought from a local healthcare librarian or information specialist with experience of conducting searches for systematic reviews. Since this thesis reports the conduct of a research study performed under supervision for award of Doctor of Pharmacy programme, the literature review was performed independently, without assistance from librarians or information specialists despite the recommendations from the Cochrane collaboration.

A literature review was planned for three aspects of interest for the present research study, namely the role of complex interventions performed by pharmacists, inhaler technique and adherence on asthma outcomes. The aim of the search strategies was to obtain as many published studies as possible within time and funding constraints. As such, search terms used within each literature review were kept as broad as possible. It was decided that all

international published studies were potentially relevant as asthma is a global health problem, and its management is similar across many countries, with similar access to medicines, inhaler devices and healthcare resources (Global Initiative for Asthma, 2014). Whilst Cochrane recommend that no language restrictions should be placed on search strategies, this is known to substantially increase the costs and time taken to complete literature reviews (Higgins and Green, 2011). Consequently the search strategies for these literature reviews had to be limited to English Language as there was no funding available for translation services.

A decision was made to perform literature searches in a variety of healthcare search engines to prevent selection bias in the literature review, as a systematic review has shown that only 30% to 80% published randomised trials may be identifiable from using MEDLINE alone (Higgins and Green, 2011). Whilst the Cochrane Central Register of Controlled Trials (CENTRAL) is considered by the Cochrane Collaboration to be the best single source of reports of trials for inclusion in Cochrane reviews, it was not available to the lead investigator and so was not used. Consequently the healthcare databases used were MEDLINE, and AMED, EMBASE, HMIC, PsycINFO, BNI, CINAHL, HEALTH BUSINESS ELITE because these are all freely accessible to NHS staff. Hand searching of references in published studies was also used to identify additional studies that had not already been identified. A decision was made to exclude the use of conference abstracts from the literature review as these often provided insufficient data. Other potential sources of grey literature were not searched, due to time and budget restraints. Web searching, such as using Google or Google Scholar, was avoided, because there is little empirical evidence to the value of using general internet search engines (Higgins and Green, 2011).

3.2.1 The effects of complex pharmacist interventions on asthma control

It is important to understand the evidence base for pharmacist-led management of asthma, and so a literature review was performed to identify controlled studies that assessed the impact of complex pharmacist interventions of any form in the management of asthma. The inclusion criteria for this literature review were quantitative randomised trials or controlled trials in which the effect of more than one intervention performed by a pharmacist in community or

hospital settings was compared to usual care of patients with asthma. All studies had to report relevant asthma outcome measures, although no restriction was placed on specific asthma outcome measures due to low number of studies identified. Studies were excluded if they recruited patients with acute exacerbations of asthma, or if they included follow-up of interventions instigated by other healthcare professionals.

Studies were identified using the healthcare databases MEDLINE, and AMED, EMBASE, HMIC, PsycINFO, BNI, CINAHL, HEALTH BUSINESS ELITE. The searches were performed on 12th June 2012 and 3rd July 2012, and then updated on 4th February 2014 and again on 9th September 2014. The search terms used were: (exp PHARMACY AND exp ASTHMA), (exp PHARMACISTS AND exp ASTHMA), (exp PHARMACY SERVICE, HOSPITAL AND exp ASTHMA), and (exp ASTHMA AND exp HEALTH CARE COSTS). Where necessary, these search strategies were limited to [Humans and (Age Groups All Adults 19 plus years)]. These searches identified 548 articles, which were reduced to 89 after review of the article titles and removal of duplicates. Screening of the abstracts identified 40 unique articles that met the inclusion criteria for full text review. Further application of the inclusion criteria was applied to these articles to identify those that truly met the inclusion criteria. The selection process was recorded as a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram (Liberati et al., 2009) (**Figure 1**).

The risk of bias was assessed for each of the nine included studies for seven separate domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other biases), using criteria outlined in the *Cochrane Handbook for Systematic Reviews* (Higgins and Green, 2011). The risk of bias was graded as high, low or unclear, with justifications for this judgement in the 'Risk of bias' table (see **Appendix 1**).

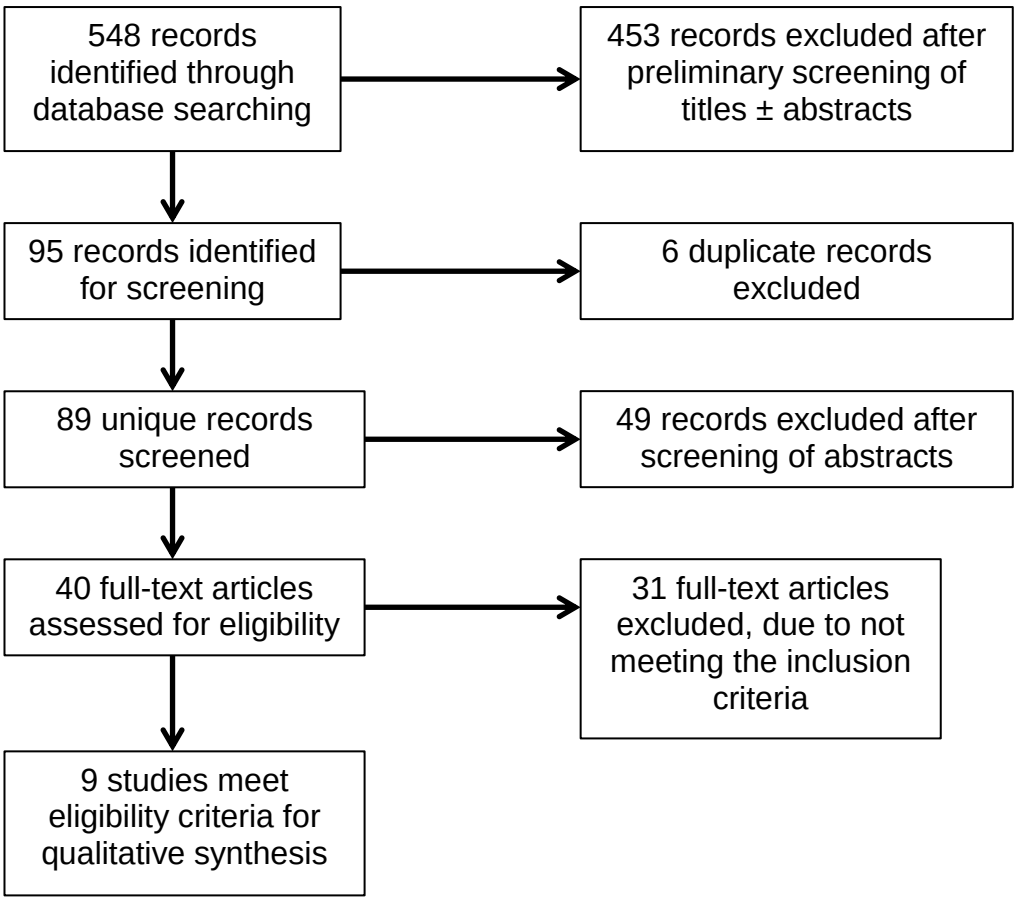


Figure 1. Study selection diagram: Literature Review on the effects of complex pharmacist interventions on asthma control.

3.2.2 Effect of inhaler technique on asthma control

Published data, outlined in the introduction (see **Chapter 2.2**) clearly demonstrates that asthma patients frequently have poor inhaler technique, which may impact on their asthma control. Consequently, it is important to determine whether inhaler technique in patients can be improved, and how this affects their asthma control. A literature review was performed to identify studies that assess the impact of interventions that were solely focused on improving inhaler technique in asthma, and the effectiveness of both this and the impact on asthma outcomes. Inclusion criteria for the literature review were quantitative studies investigating the effect of interventional and educational strategies specifically targeting only inhaler technique on (i) improvement in overall inhaler technique, and (ii) asthma control and health status. Due to limited numbers of studies that met these inclusion criteria, studies were not

restricted to randomised controlled trials. Studies were excluded where inhaler technique training comprised one of several interventions, since this could confound study outcomes.

Studies were identified using the healthcare database MEDLINE, and AMED, EMBASE, HMIC, PsycINFO, BNI, CINAHL, HEALTH BUSINESS ELITE and were performed on 17th July 2012, 25th March 2014, and 9th September 2014. The search terms were as follows: (exp NEBULIZERS AND VAPORIZERS AND exp ADMINISTRATION, INHALATION AND technique.ti,ab). Where necessary, these search strategies were limited to [English Language and Humans].

These searches identified 347 articles, which were reduced to 99 after review of the article titles and removal of duplicates. Review of the reference lists identified a further 39 studies. Screening of this total of 138 abstracts identified 45 articles that met the inclusion criteria for full text review. Further application of the inclusion criteria was applied to these articles to identify those that completely fulfilled the inclusion criteria. The selection process was recorded as a PRISMA (Liberati et al., 2009) flow diagram (**Figure 2**).

The risk of bias was assessed for each of the six included studies for seven separate domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other biases), using criteria outlined in the *Cochrane Handbook for Systematic Reviews* (Higgins and Green, 2011). The risk of bias was graded as high, low or unclear, with justifications for this judgement in the 'Risk of bias' table (see **Appendix 2**).

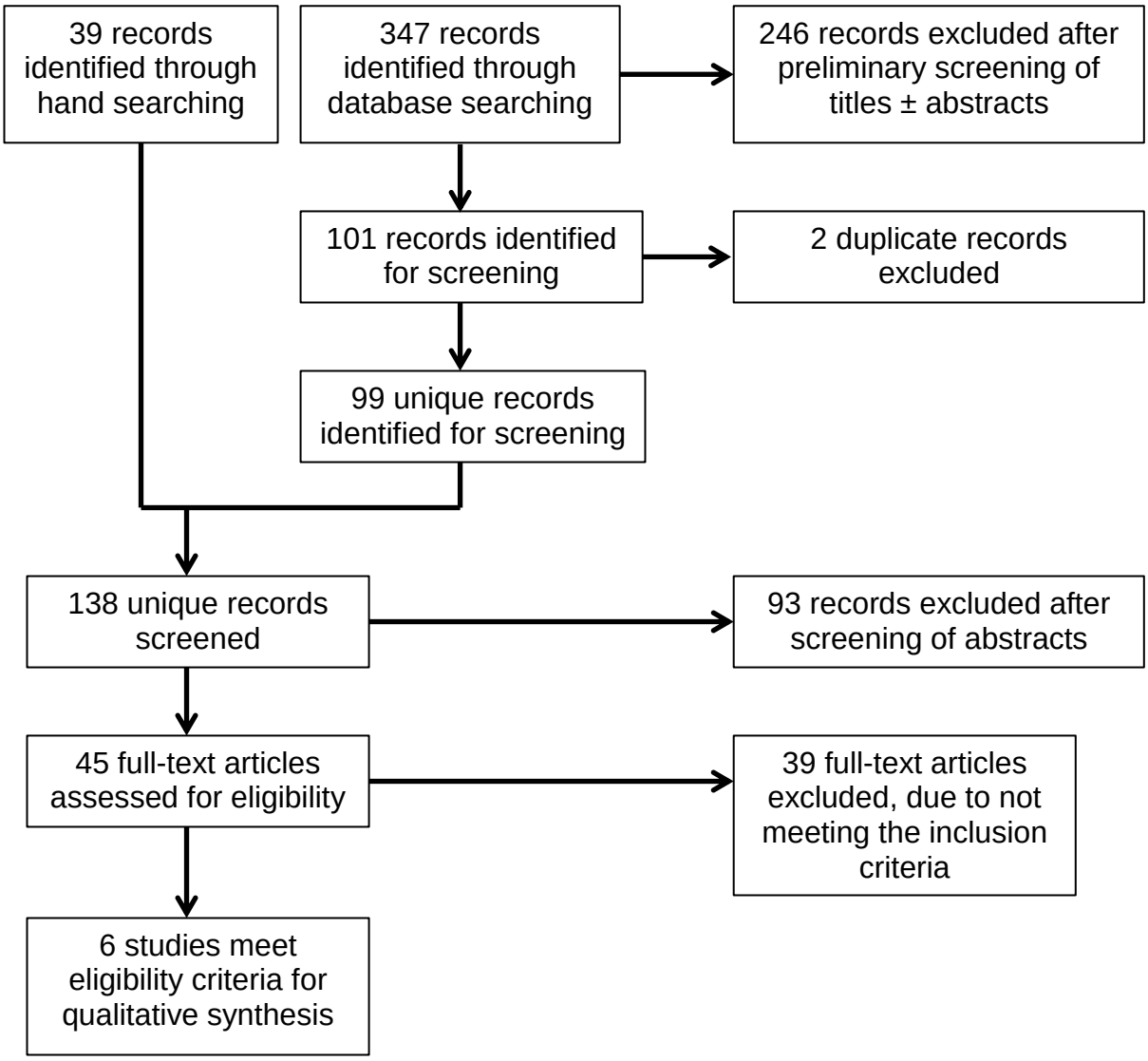


Figure 2. Study selection diagram: Literature Review on the effect of inhaler technique on asthma control.

3.2.3 The effect of interventions to improve adherence to inhaled corticosteroids on asthma control

Since published data, outlined in the introduction (see **Chapter 2.3**) clearly demonstrate an association between adherence to ICS and asthma control, it is important to determine whether interventions designed to improve adherence may improve asthma outcomes. A literature search was performed to examine this, with inclusion criteria comprising studies that investigate the effect of interventional and educational strategies specifically targeting adherence to ICS on (i) improvement in overall adherence, and (ii) asthma control or health

status. Studies were excluded from the literature review if they investigated adherence only to asthma medicines other than ICS, where no interventions were made, or if they only performed qualitative analysis of adherence.

Studies were identified using the healthcare database MEDLINE, and searches were performed on 3rd July 2012 and repeated on 18th September 2012, 4th February 2014 and again on 9th September 2014. The search terms used were (exp MEDICATION ADHERENCE AND exp ASTHMA), and were limited to [English Language and Humans AND (Age Groups All Adults 19 plus years)]. This search was repeated on other healthcare databases on 4th February 2014, and 9th September 2014 using: AMED, EMBASE, HMIC, PsycINFO, BNI, CINAHL, and HEALTH BUSINESS ELITE. These searches found a total of 682 articles, which were reduced to 115 after review of the article titles and removal of duplicates. Screening of the abstracts of each of these articles identified 49 that appeared to meet the literature review inclusion criteria, and full-text was obtained for detailed assessment. The selection process was recorded as a PRISMA (Liberati et al., 2009) flow diagram (**Figure 3**).

The risk of bias was assessed for each of the six included studies for seven separate domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other biases), using criteria outlined in the *Cochrane Handbook for Systematic Reviews* (Higgins and Green, 2011). The risk of bias was graded as high, low or unclear, with justifications for this judgement in the 'Risk of bias' table (see **Appendix 3**).

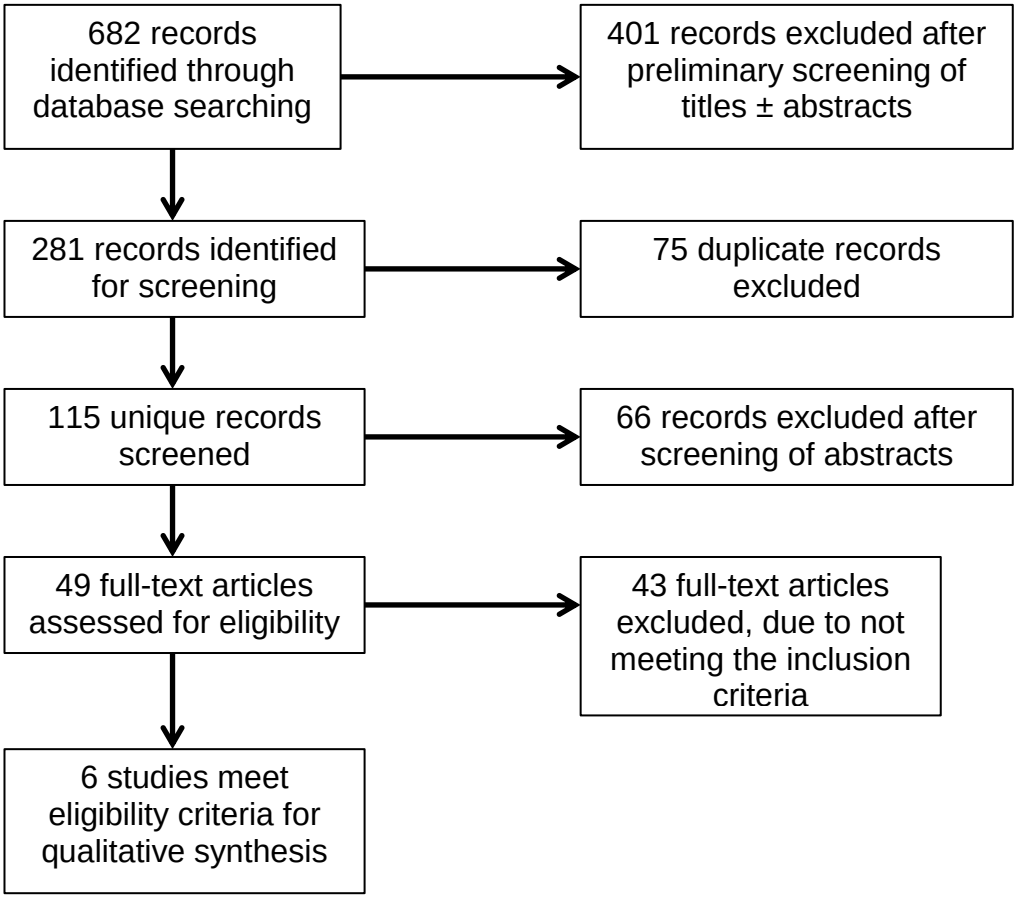


Figure 3. Study selection diagram: Literature Review on the effect of interventions to improve adherence to inhaled corticosteroids on asthma control.

3.3 Literature review and critical analysis

3.3.1 The effects of complex pharmacist interventions on asthma control

3.3.1.1 Results of the search

After screening of study titles and abstracts, and removal of duplicates, 40 full-text articles were retrieved for consideration for review, and nine were found to meet the eligibility criteria (see **Figure 1**).

3.3.1.2 Included studies

See Characteristics of included studies (**Appendix 1**) for details. A total of nine articles met the inclusion criteria for the literature review (Armour et al., 2007, Barbanel et al., 2003, Charrois et al., 2006, Cordina et al., 2001, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Mehuys et al., 2008, Petkova, 2008,

Saini et al., 2008), and are summarised in **Table 1**. All nine studies were based in community pharmacies (range one to 66 pharmacies per study). No studies that met the inclusion criteria reported the effects of complex interventions performed by secondary care pharmacists, and similarly no studies were found that sought to exclusively recruit patients who are classed as having difficult asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014).

Two studies did not report the level of asthma control or severity of symptoms of recruited patients (Barbanel et al., 2003, Cordina et al., 2001), two used the severity classification from the National Asthma Council Australia (Armour et al., 2007, Saini et al., 2008), two used ACQ (Charrois et al., 2006, Garcia-Cardenas et al., 2013), one used the ACT (Mehuys et al., 2008), one used severity based on an unreferenced Expert Panel Report 2: Guidelines for diagnostic and management of asthma, 1997 (Petkova, 2008), and one used an apparently un-validated and unreferenced measure of asthma severity (Kritikos et al., 2007). Four studies reported the proportion of patients with severe asthma symptoms; ranging from 30% of patients in one study (Petkova, 2008), to 71-88% in another (Armour et al., 2007). However three studies only reported the mean level of asthma control using different scoring systems (Charrois et al., 2006, Mehuys et al., 2008, Saini et al., 2008). Due to the variety of methods of reporting asthma severity or control, it is not possible to standardise or compare the extent of impact of pharmacist interventions on asthma outcomes across the nine studies included in the literature review.

3.3.1.3 Excluded studies

Thirty one studies did not meet the literature review inclusion criteria for a variety of reasons including: lack of relevant asthma outcome data (6 articles) (Saini et al., 2011b, Smith et al., 2007, Takemura et al., 2012, Hinchageri et al., 2012, Rathan Shyam et al., 2013, Ovchinikova et al., 2011), study design (e.g. non-quantitative methodology, lack of comparative arm or control group, non-randomised controlled study, systematic review) (9 articles) (Emmerton et al., 2003, Mangiapane et al., 2005, Saini et al., 2011a, Saini et al., 2006, Stiegler et al., 2003, Watanabe et al., 1998, Adunlin and Mahdavian, 2012, Benavides et al., 2009, Armour et al., 2013), mixed healthcare professional interventional

studies (3 articles) (Knoell et al., 1998, Pauley et al., 1995, Wang et al., 2010), study not being fully published (3 articles) (Basheti et al., 2007, Lim et al., 2012, Murphy et al., 2012a), wrong age group due to recruitment of children (2 articles) (Munzenberger and Hill, 2007, Petrie and Segal, 2010), articles that were not research studies (2 articles) (Kelly, 2006, Wittbrodt et al., 2006), intervention performed on different long term conditions or in addition to asthma (2 articles) (Pizzi et al., 2001, Weinberger et al., 2002), implementation of a single rather than a complex intervention (3 articles) (Simpson et al., 2004, Giraud et al., 2011, Basheti et al., 2008), lack of reporting of inclusion or exclusion criteria (1 article) (McLean et al., 2003), and incomplete data reporting (1 article) (McLean et al., 2003).

3.3.1.4 Interventions

See summary table of complex pharmacist interventions on asthma control (**Table 1**) and Characteristics of included studies (**Appendix 1**) for details.

The complex interventions performed in these nine studies were broadly similar and content included patient education (eight studies (Armour et al., 2007, Barbanel et al., 2003, Charrois et al., 2006, Cordina et al., 2001, Kritikos et al., 2007, Mehuys et al., 2008, Petkova, 2008, Saini et al., 2008)), medication review and/or inhaler technique assessment (nine studies (Armour et al., 2007, Barbanel et al., 2003, Charrois et al., 2006, Cordina et al., 2001, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Mehuys et al., 2008, Petkova, 2008, Saini et al., 2008)), asthma review including assessment of asthma control (four studies (Armour et al., 2007, Cordina et al., 2001, Garcia-Cardenas et al., 2013, Saini et al., 2008)), adherence assessment (three studies (Armour et al., 2007, Garcia-Cardenas et al., 2013, Mehuys et al., 2008)), self-management education and provision of action plan (five studies (Armour et al., 2007, Barbanel et al., 2003, Charrois et al., 2006, Petkova, 2008, Saini et al., 2008)).

All but one study had at least a 3-month follow-up period following the initial pharmacist intervention (range 12 weeks to 12 months), with a 6-month duration in five studies. The mean number of patients recruited to each of the studies was 156 (range 24 to 396), and seven studies recruited 50 or more patients. All nine studies ensured that community pharmacists providing the interventions

under investigation were adequately trained. The duration of training ranged from a half-day workshop to a three day multidisciplinary course, but all appeared to have similar content comprising aspects of education on asthma pathophysiology, assessment and monitoring, medications, inhaler technique, adherence, lifestyle modifications and patient education and self-management. The broad similarities shown for pharmacist training demonstrates that education of healthcare professionals is an important aspect in the study design of pharmacist interventional studies, and has been found to have a positive impact on the behaviour of intervention pharmacists in these studies (Saini et al., 2006).

3.3.1.5 Primary outcomes

See summary table of complex pharmacist interventions on asthma control (**Table 1**) and Characteristics of included studies (**Appendix 1**) for details.

The primary outcome was a measure of asthma control or asthma severity in six studies: National Asthma Council Australia asthma severity (Armour et al., 2007, Saini et al., 2008), ACQ (Charrois et al., 2006, Garcia-Cardenas et al., 2013), ACT (Mehuys et al., 2008), or a validated North of England asthma symptoms scale (Barbanel et al., 2003). One study used Quality of life (measured using the Short Form (SF)-36 and Living with Asthma Questionnaire (LWAQ)) as the primary outcome (Cordina et al., 2001), one used inhaler technique (Kritikos et al., 2007), whilst another did not specify a primary outcome measure (Petkova, 2008). Common secondary outcome measures included quality of life measures (most frequently AQLQ), lung function, inhaler technique and adherence. The method of reporting inhaler technique varied, with some studies reporting percentage scores (Cordina et al., 2001, Mehuys et al., 2008, Saini et al., 2008), whilst others reported the proportion of patients with optimal technique (Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Petkova, 2008, Armour et al., 2007). Similarly, adherence was measured using a variety of methods including prescription records (Armour et al., 2007, Mehuys et al., 2008), self-reporting (Cordina et al., 2001), or questionnaires (Armour et al., 2007, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Saini et al., 2008).

3.3.1.6 Risk of bias

The assessment and justification of the risk of bias for each of the included studies is presented in the Characteristics of included studies (**Appendix 1**). All studies had at least one domain where there was assessed to be a potential high risk of bias, primarily because outcome assessments did not appear to blinded in all but one study. Four studies were at high risk of bias as there was no blinding of participants and personnel and there could be a high risk of contamination of usual care (Barbanel et al., 2003, Charrois et al., 2006, Mehuys et al., 2008, Petkova, 2008).

Table 1. Brief summary of the effect of complex pharmacist interventions on asthma control

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Armour et al., 2007), Australia	To evaluate the effect of the Australian Pharmacy Asthma Care Program on asthma control and other clinical and humanistic outcomes.	Design: multi-site randomised intervention versus control study. N: 396. Duration: 6 months.	Pharmacy Asthma Care Program protocol: assessing asthma control, targeted counselling and education on asthma, medication and lifestyle issues, review of inhaler technique, adherence, detection of drug-related problems, goal setting and referral to GP as appropriate. The control group received usual care only.	Primary: Change in asthma control Secondary: Adherence, SABA use, quality of life, asthma knowledge.	The proportion of patients with severe asthma declined in the PI group (87.9% to 52.7%, $p<0.001$), but was unchanged in the UC group (71.2% to 67.9%, $p=0.11$). Greater improvement in AQLQ in the PI vs. UC group ($p<0.05$), adherence ($p=0.03$), and SABA use ($p<0.03$).	Pharmacists in the intervention group received training and education on asthma and its management. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Barbanel et al., 2003), London	To test whether community pharmacists can improve asthma control with self-management advice	Design: randomised controlled study. N: 24. Duration: 3 months.	Patient education, assessment of inhaler technique, and self-management advice based on peak expiratory flow measurements and symptoms, with weekly telephone follow-up. The control group received usual care only.	Primary: asthma health status, measured using the North of England asthma symptoms scale.	Significant improvement in patients in the intervention compared to the control group (7.0, $p<0.001$).	Pharmacists in the intervention group received training and education on asthma and its management. Intervention performed in community pharmacies.
(Charrois et al., 2006), Canada	To determine whether community pharmacists could improve asthma control in a rural setting.	Design: randomised controlled study. N: 70. Duration: 6 months.	Educational program on asthma, action plan, assessment of asthma therapy, and referral to a respiratory therapist and primary care physician as needed. The control group patients received an asthma education booklet and general advice as needed.	Primary: change in ACQ. Secondary: use of ICS, change in FEV_1, courses of oral steroids, hospital admissions.	Mean change in ACQ: 0.33 and 0.43 in the control and intervention groups (no significant difference between the 2 groups, $p = 0.66$). No significant difference for any secondary outcome.	All pharmacists received training and education on asthma and its management. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Cordina et al., 2001), Malta	To examine the impact of a community pharmacy-based education and monitoring program on asthma outcomes.	Design: randomised controlled prospective trial. N: 152. Duration: 12 months.	Comprehensive asthma education and monitoring program, including information on asthma pathology, triggers, use of inhaler devices and peak flow meters. The control group received routine dispensing only.	Primary: Quality of life using SF-36 and LWAQ. Secondary: Peak expiratory flow (PEF), inhaler technique, compliance,	No significant differences between the 2 groups on SF-36 or LWAQ, although there was a significant improvement at 12 months on LWAQ in the intervention group. PEF unchanged in the intervention group, but worse in the control group. Significant improvement in inhaler technique in intervention group. There was no difference in self-reported adherence.	Pharmacists in the intervention group received training and education on asthma and its management. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Garcia-Cardenas et al., 2013), Spain	To evaluate the effect of a pharmacist intervention on asthma control	Design: cluster randomised trial. N: 346. Duration: 6 months.	Protocol-based intervention addressing individual needs related to asthma control, inhaler technique and adherence. The control group received usual care only.	Primary: ACQ Secondary: inhaler technique, adherence.	Significant improvement in ACQ in the intervention group (-0.66, p<0.001), but not in the control group (-0.15 (p value not reported). Higher proportion of patients with correct Turbohaler inhaler technique and adherence at 6 months in the intervention group.	Pharmacists in the intervention group received training and education on asthma and its management. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Kritikos et al., 2007), Australia	To compare the effects of asthma education interventions provided by a pharmacist, a pharmacist educator, or usual community pharmacist care on asthma outcomes.	Design: parallel group pilot study. N: 48. Duration: 12 weeks.	Education on asthma, its management, asthma medication, inhaler use, and relevant written information. The control group received the same written information without additional education.	Primary: no primary outcome measure was specified Secondary: inhaler technique, asthma severity, AQLQ, adherence.	Significant reduction in percentage of patients with severe asthma / poor control at 12 weeks in the two pharmacist intervention arms compared to usual care (25% and 13% vs. 50%, p=0.04). Significant increase in the proportion of patients with optimal pMDI and DPI technique and improvement in AQLQ at 12 weeks in intervention groups. There was no difference in adherence at 12 weeks.	Pharmacists in the intervention group received training and education on asthma and its management. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Mehuys et al., 2008), Belgium	To determine whether pharmacist Interventions would result in improved asthma control.	Design: randomised, controlled, parallel-group trial. N: 201. Duration: 6 months.	Education on inhaler technique, asthma symptoms, triggers and warning signs, understanding medication, adherence and smoking cessation. The control group received usual care only.	Primary: ACT Secondary: PEF, SABA use, inhaler technique, adherence.	Mean ACT was unchanged in both groups, however in patients insufficiently controlled at baseline, a significant improvement was seen (mean difference 2.0 vs. control, p=0.038). Improvement in adherence and inhaler technique, and reduction in SABA use in the intervention group.	All pharmacists received training and education on asthma and its management. Intervention performed in community pharmacies.
(Petkova, 2008), Bulgaria	To evaluate the effect of education programs provided by community pharmacists on quality of life.	Design: randomised controlled trial. N: 50. Duration: 4 months.	Educational program on asthma, triggers, exercise, self-management, smoking-cessation, treatment, inhaler technique, and side effects. The control group received usual care only.	Primary: no primary outcome measure was specified Secondary: quality of life (assessed through an adapted disease-specific instrument Asthma Assessment form, PEF, inhaler technique.	Improvement in quality of life in the intervention group (from 3.55 to 3.77 on a 5-point scale, p<0.0001), but was reduced in the control group (from 3.39 to 3.00, p=0.039). No effect on PEF. Inhaler technique data is inadequate to make conclusions.	All pharmacists received training and education on asthma and its management. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Saini et al., 2008), Australia	To compare the effect of a pharmacist-delivered asthma service on asthma outcomes compared to standard care.	Design: parallel group, controlled repeated measures study. N: 51. Duration: 6 months.	Intensive pharmacist education (assessment of asthma severity, medication and inhaler use, performing spirometry, providing Action Plan, and education, and making appropriate interventions). The control group received usual care only.	Primary: Asthma severity score calculated using the Australian National Asthma Council's asthma severity classification. Secondary: inhaler technique, adherence, quality of life.	Significant improvement in asthma severity score in the intervention group compared to usual care (reduction in score of 3.6 vs. 0.09; $p<0.001$ in the as per protocol analysis). Significant reduction in the risk of non-adherence. No effect on SABA use or quality of life. Improvement in inhaler technique scores for pMDI, Accuhaler and Turbohaler devices.	Pharmacists in the intervention group received training and education on asthma and its management. Intervention performed in community pharmacies.

3.3.1.7 Effects of interventions

See summary table of complex pharmacist interventions on asthma control (**Table 1**) and Characteristics of included studies (**Appendix 1**) for details.

The two studies that used the Australian National Asthma Council asthma severity assessment table to determine the outcome of the complex pharmacist interventions, demonstrated statistically significant improvements in asthma severity after six-months follow-up (Armour et al., 2007, Saini et al., 2008). These two studies recruited a population with high rates of severe asthma symptoms; in one study 71-88% of patients had severe asthma symptoms (Armour et al., 2007), whilst in the other the mean asthma severity score was 10.3 and 11.4 (on a 5- (mild) to 15-point (severe) scale) in the control and intervention groups respectively (Saini et al., 2008).

The two six-month studies that used ACQ as a measure of asthma control failed to demonstrate a significant impact of complex pharmacist interventions compared to control in the overall population (Charrois et al., 2006, Garcia-Cardenas et al., 2013). One study recruited patients considered to be at high risk, defined as those with recent admissions to hospital, attendance at the emergency department, or using at least 2 canisters of inhaled beta$_2$-agonist in the previous 6 months. At baseline the mean ACQ was 1.45 to 1.91 but only 69% to 77% of patients were prescribed an ICS (Charrois et al., 2006), suggesting either that many patients had an incorrect self-reported diagnosis, or had only mild symptoms. This study found no improvement in any asthma outcome measure, although the authors reported that this might have been due to poor uptake of the intervention or contamination of the usual care group. In the second study, 55-72% of recruited patients were uncontrolled at baseline (Garcia-Cardenas et al., 2013), and when the improvement in ACQ was measured for only those patients with uncontrolled asthma at baseline, a statistically significant and clinically important improvement in ACQ was found. A similar finding was noted in the study using ACT to measure change in asthma control six-months after the complex pharmacist intervention (Mehuys et al., 2008), where no significant improvement was observed in the overall patient population, but was observed in those patients with uncontrolled asthma at baseline. Barbanel *et al* (2003) used the 'North of England asthma symptoms

scale' as a validated instrument to measure asthma related health status, and found a clinically meaningful improvement in asthma symptom scores at three-months (Barbanel et al., 2003).

The only study to use quality of life as the primary endpoint failed to demonstrate a significant benefit in terms of general health or asthma-specific quality of life (Cordina et al., 2001). However two studies using AQLQ as a validated measure of asthma-related quality of life as a secondary outcome measure demonstrated significant improvements in patients randomised to complex pharmacist interventions compared to usual care (Armour et al., 2007, Kritikos et al., 2007). In contrast, a third study failed to demonstrate any significant effect of pharmacist interventions on AQLQ in the overall patient population (Mehuys et al., 2008), but may have been confounded by the presence of well controlled patients in the population, which would also explain the failure of other studies to demonstrate significant benefits using un-validated measures of quality of life (Petkova, 2008).

A further benefit of complex pharmacist interventions, consistently demonstrated across randomised trials, was a significant improvement in inhaler technique compared to patients in control groups (Cordina et al., 2001, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Mehuys et al., 2008), which may contribute to positive asthma outcomes such as asthma control and quality of life (see **Chapter 3.3.3**). The different methods used to rate inhaler technique makes direct comparison between the studies difficult (Basheti et al., 2014), because some reported percentage of steps performed correctly, whilst others reported percentage of patients with optimal inhaler technique.

In summary, the literature review on the effect of complex pharmacist interventions on asthma outcomes is limited by a number of factors, in particular the heterogeneity of study designs comprising a variety of different individual interventions and varying follow-up schedules ranging from weekly telephone follow-up interviews, to monthly follow-up reviews, or just two follow-up sessions. A further limitation of many of the studies was that there was assessed to be a high risk of bias introduced into the study design, through unclear randomisation methods and the nature of the interventional study

preventing any blinding into the intervention and assessment. Most studies were considered to have a low risk of contamination bias as most studies randomised patients by recruiting community pharmacists to provide only the interventions being studied or to provide usual care. Contamination bias can be a significant concern, as in one study where there was a risk of contamination between intervention and control patients within the same community pharmacy, no significant impact was observed on asthma control or quality of life (Mehuys et al., 2008).

The short duration of some of the studies (three had a duration of less than six months), which also had relatively small patient populations (Barbanel et al., 2003, Kritikos et al., 2007, Petkova, 2008), may be of concern in a literature review where the other studies are all of at least six months in duration. This is because short, small studies may not allow an adequate reflection of the variable nature of asthma, and consequently may not be sufficiently powered to allow an accurate assessment of the effects on asthma control or exacerbations, where these data may be skewed by the changes in clinical condition due to the variable nature of asthma rather than a true effect of the intervention, or vice versa.

A limitation of the literature review was that the inclusion criteria limited studies to those that had a control arm, and so several pre-post intervention prospective studies that demonstrate significant benefits of complex pharmacist interventions, but without a control arm, were excluded (Armour et al., 2013, Emmerton et al., 2003, Mangiapane et al., 2005).

The overall consensus from the studies included in the literature review is supportive of complex interventions performed by community pharmacists in managing asthma, apparently when targeted at patients with uncontrolled asthma who have the greatest potential to benefit. Studies that recruited a large proportion of people with asthma who were reasonably well controlled reported less favourable results, which is unsurprising considering their baseline health status. These findings justify recommendations from the BTS/SIGN and GINA guidelines, which recommend that all patients with asthma should be offered, what should be considered as a complex intervention comprising self-

management education, reinforced with a written asthma action plan as this can reduce healthcare resource utilisation (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014). Asthma education recommendations are consequently complex, and include the nature of asthma and its treatment, how to use prescribed medication, how to undertake self-monitoring, developing a written personalised asthma action plan, recognition and management of acute exacerbations and allergen or trigger avoidance (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014). The provision of a personalised asthma action plan is an important component of asthma management, since the failure to provide an action plan may be associated with an increased risk of asthma deaths (Royal College of Physicians, 2014).

3.3.2 Medicines use reviews

Since 2005, UK community pharmacists have been funded to provide MURs for patients with long-term conditions. Asthma has been listed as one of the NHS national target groups for MUR services since October 2011 (Department of Health, 2013). All asthma patients are eligible for one t-MUR per year if they have received pharmaceutical services from the same pharmacy for at least three consecutive months (Department of Health, 2013).

As there have been no large randomised controlled studies assessing the impact of MUR services in asthma, a thorough literature review has not been performed for this thesis. However it is important to summarise and understand the current literature in order to appreciate how and why the MUR service might be incorporated into the present research study.

A number of audits have demonstrated that a large proportion of MURs result in either interventions or advice being provided, highlighting the value of this service to improve patients' knowledge and use of drugs (Department of Health, 2013). One such audit of ten MUR forms collected from each of ten pharmacies within Brighton and Hove Primary Care Trust, found that recommendations were made in 81% of MURs, and the patient was referred to the GP in 18% of cases (MacAdam and Sherwood, 2011); whilst a second audit of 464 MUR forms from 15 community pharmacies found that 24.7% had lifestyle

recommendations, 23.4% identified drug interactions or contra-indications, 34.8% reported adherence problems, 32.9% advised review by the GP, and 3.2% gave advice on synchronising repeat prescriptions (van den Berg and Donyai, 2010).

There have been a small number of studies that have assessed the value of MURs in asthma patients, and have consistently demonstrated that they are a useful service to improve asthma management. An early prospective analysis of asthma MUR interventions by 47 community pharmacies in Hampshire and the Isle of Wight sought to describe and evaluate this service over a 6 month period (Portlock et al., 2009). Components of the MUR included inhaler technique and adherence assessments, and were performed in a total of 965 patients. 37% of patients demonstrated primary non-adherence (defined as less than 75% of prescriptions collected within the past 12 months), and all these patients also had secondary adherence problems (described as being due to beliefs about medicines, due to inhaler device issues, or due to medicines issues). Of the 607 patients collecting more than 75% of their prescriptions, 300 reported similar secondary adherence issues. Overall, pharmacists made a total of 1,787 interventions, of which 41% were device checks, 10% were GP or nurse referral and 49% were educational. This study also demonstrated that MURs were well accepted by asthma patients, but no assessment of effect on asthma control or symptoms was performed to determine the impact of any interventions.

A second study published in abstract form, assessed the impact on asthma control using the ACT in 154 patients after an asthma MUR (Bagole et al., 2007). All patients received their MUR in person with subsequent assessment of asthma control by telephone interview. 44% of patients completed the telephone interview, 15% declined to participate, whilst 41% could not be contacted. The mean ACT score improved from 17.2 to 18.8 ($p = 0.0048$) after MUR. The proportion of patients with controlled asthma increased from 5% to 9%, and reasonably controlled asthma increased from 36% to 46%, whilst those who were not controlled decreased from 59% to 45% ($p=0.0074$). The asthma MUR service was rated as very good by 73% of patients, and good by 21%.

A recent large audit across the South Central region in England reported a 40% increase in the proportion of patients with reasonably well-controlled asthma (measured using ACT) between a first and second MUR, where there was an extra emphasis on improving inhaler technique (The Cambridge Consortium, 2012). However, this audit has severe limitations in that the follow-up period was not reported and no explanation was provided to account for why only 596 of 4,004 patients underwent a follow-up MUR and asthma control assessment. It is therefore uncertain whether the data provided were an interim analysis or whether there was a high discontinuation rate, and how this may have affected the overall results.

Studies in asthma patients have demonstrated that MURs are well accepted, and can identify and manage adherence problems and potentially may improve asthma control (Bagole et al., 2007, Portlock et al., 2009).

3.3.3 Effect of inhaler technique training on asthma control

3.3.3.1 Results of the search

After screening of study titles and abstracts, and removal of duplicates, 45 full-text articles were retrieved for consideration for review, and six were found to meet the eligibility criteria (see **Figure 2**).

3.3.3.2 Included studies

See Characteristics of included studies (**Appendix 2**) for details. Six studies met the inclusion criteria for the literature review (Al-Showair et al., 2007, Alamoudi, 2003, Ammari and Chrystyn, 2013, Basheti et al., 2008, Basheti et al., 2005, Giraud et al., 2011).

The studies varied in study design, setting and duration, ranging from two weeks to six months. Two studies were six-week controlled trials assessing different methods for correcting IFRs on inhaler technique and quality of life, of which one was based in a hospital outpatient clinic (Al-Showair et al., 2007) and one based in community pharmacies (Ammari and Chrystyn, 2013). A third study was a two-week pilot study examining different methods of inhaler technique training in community pharmacy settings (Basheti et al., 2005), which followed on to a second larger six-month single-blind cluster randomised

parallel group study examining the effect of inhaler technique training in community pharmacies on lung function, inhaler technique and asthma control (Basheti et al., 2008). The final two studies were uncontrolled prospective studies, one of which assessed the effects of training on improving inhaler technique in hospital outpatients (Alamoudi, 2003), and the other examined the impact on asthma control over one month in community pharmacies (Giraud et al., 2011).

3.3.3.3 Excluded studies

Seven studies were found to provide cross-sectional data on inhaler technique in asthma patients (Adeyeye and Onadeko, 2008, Baddar et al., 2014, Giraud and Roche, 2002, Hardwell et al., 2011, Levy et al., 2013, Melani et al., 2011, Roy et al., 2011), and ten provided data in inhaler technique in healthcare professionals (Baddar et al., 2001, Basheti et al., 2009, Baverstock et al., 2010, Cain et al., 2001, Hanania et al., 1994, Interiano and Guntupalli, 1993, Jackevicius and Chapman, 1999, Jones et al., 1995, Resnick et al., 1996, Toumas et al., 2009).

A further 22 studies were did not meet the inclusion criteria for a variety of reasons including: policy document (one paper (Laube et al., 2011)), review article (eight papers (Azouz and Chrystyn, 2012, Basheti et al., 2014, Capstick and Clifton, 2012, Chrystyn, 2003, Chrystyn and Price, 2009, Crompton et al., 2006, Haughney et al., 2010, Price et al., 2013)), mixed respiratory disease (five papers (Chorão et al., 2014, Lavorini et al., 2008, Melani et al., 2004, Molimard et al., 2003, Press et al., 2012)), Editorial (one paper (Nikander, 2010)), study objectives did not meet literature review criteria and had incomplete outcome data (one paper (Goodyer et al., 2006)), no outcome data (six papers (Brennan et al., 2005, Campos et al., 2006, Ovchinikova et al., 2011, Press et al., 2012, Takemura et al., 2010, The Cambridge Consortium, 2012)). One study, published as an investigation on the potential impact of inhaler technique on asthma control, was confounded by multiple additional interventions performed during hospital clinic appointments and so was also excluded from the literature review (Harnett et al., 2014).

3.3.3.4 Interventions

See summary table of the effects of inhaler technique training on asthma control (**Table 2**) and Characteristics of included studies (**Appendix 2**) for details.

All six studies provided verbal instructions on correct inhaler technique, but only three reinforced this with demonstration by the healthcare professional providing the training (Alamoudi, 2003, Basheti et al., 2008, Basheti et al., 2005). Two studies also provided written instructions (Basheti et al., 2008, Giraud et al., 2011) and two provided training aids in the form of a 2Tone Trainer whistle (Al-Showair et al., 2007, Ammari and Chrystyn, 2013).

Inhaler technique education was provided by a pharmacist in three studies (Basheti et al., 2008, Basheti et al., 2005, Giraud et al., 2011), a nurse in one study (Alamoudi, 2003), the lead researcher in one study (Ammari and Chrystyn, 2013), but was uncertain who provided the education in the other study (Al-Showair et al., 2007).

3.3.3.5 Primary outcomes

See summary table of complex pharmacist interventions on asthma control (**Table 2**) and Characteristics of included studies (**Appendix 2**) for details. The primary outcome was only specified in one study (Basheti et al., 2008), which used peak flow variability. In terms of secondary outcomes, all but one study reported inhaler technique (Al-Showair et al., 2007), and only two reported objective measures of peak IFR (Al-Showair et al., 2007, Ammari and Chrystyn, 2013). Two studies measured the effect of the intervention on asthma control (Basheti et al., 2008, Giraud et al., 2011), two measured the effect on quality of life (Al-Showair et al., 2007, Ammari and Chrystyn, 2013), one other study measured the effect on lung function (Alamoudi, 2003), and one also reported adherence (Giraud et al., 2011).

3.3.3.6 Risk of bias

The assessment and justification of the risk of bias for each of the included studies is presented in the Characteristics of included studies (**Appendix 2**).

Two studies were judged to be at high risk of bias as they were prospective observational studies with no control arm (Alamoudi, 2003, Giraud et al., 2011). Of the remaining studies, all had at least one domain where there was assessed to be a potential high risk of bias, primarily because outcome assessments did not appear to be blinded. Only one study was considered to be of low risk of bias (Basheti et al., 2008), although this study failed to report data on the primary outcome measure.

Table 2. Brief summary of the effect of inhaler technique training on asthma control

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Al-Showair et al., 2007), England	To determine whether a 2Tone Trainer [2T]; Canday Medical Ltd; Newmarket, UK) helps to maintain the correct inhaler technique.	Design: randomised controlled trial. N: 108. Duration: 6 weeks.	Measurement of peak IFR using In-Check DIAL, and assessment of pMDI inhaler technique. Patients with fast peak IFR randomised to verbal training (VT) or verbal training plus provision of a 2Tone trainer inhaler (2T). Patients with good inhaler technique (GT) received no intervention.	Primary: none stated. Secondary: peak IFR at 6 weeks, AQLQ.	At 6 weeks, there was an increase in the proportion of patients with a correct peak IFR through a pMDI in both the VT (increased from 0 to 23/35 [66%], p<0.001) and 2T groups (increased from 0 to 35/36 [97%), p<0.001). Improvements in AQLQ were demonstrated; 14 VT patients had a change >0.5 points and three >1; 22 2T patients had a change >0.5 points and 8 >1. None of the GT patients achieved a significant improvement in AQLQ.	It is unclear who performed the intervention in this study. Intervention performed in hospital outpatient clinics.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Alamoudi, 2003), Saudi Arabia	To assess whether educational programs can improve inhaler technique; and whether this may be associated with PEF measurements.	Design: prospective open study. N: 130. Duration: 6 to 8 weeks.	Education and demonstration on correct inhaler technique, for approximately 15-20 minutes. There was no control group.	Primary: none stated. Secondary: inhaler technique, PEF.	Education resulted in a significant reduction in errors in inhaler technique from 2.8 to 1.0 ($p<0.001$) for pMDI and from 0.76 to 0.081 ($p=0.002$) for Turbohaler. Increase in mean PEF from 312.4 L/min to 331.0 L/min ($p=0.003$).	No control group. Intervention performed by a nurse in hospital outpatient clinics.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Ammari and Chrystyn, 2013), England	To investigate if methods to train patients to use a slow IFR with their pMDI would improve and maintain good pMDI use.	Design: parallel-grouped clinical study. N: 50. Duration: 6 weeks.	Measurement of peak inhalation flow (IFR) using In-Check DIAL, and assessment of pMDI inhaler technique. Patients with a fast IFR (>90 L/min) were randomised to either verbal counselling (VC) or verbal counselling plus provision of a 2Tone trainer inhaler (2T). The control (CT) group received no intervention.	Primary: none stated. Secondary: peak IFR at 6 weeks, inhaler technique, AQLQ.	In adults, the change in IFR between baseline and 6 weeks in the VT and 2T groups was a median –143.5 ($p<0.001$), and –165.0 ($p<0.001$) respectively, compared to +12L/min in the CT group. Significant reduction in the median number of mistakes using pMDI in both the VT (from 5.5 to 0, $p<0.01$) and 2T groups (from 5 to 1; $p<0.01$), but no change in the control group. Improvements in quality of life were achieved in both intervention groups.	The intervention was performed by the lead researcher. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Basheti et al., 2005), Australia	To compare the effect of three counselling methods provided at the community pharmacies on Turbuhaler technique	Design: pilot study. N: 26. Duration: 2 weeks.	Turbohaler inhaler technique training by one of three methods: verbal counselling using patient information leaflet vs. augmented counselling (patient information leaflet with emphasis on essential steps) vs. augmented counselling plus demonstration. There was no control group.	Primary: none stated. Secondary: inhaler technique.	At baseline 0/26 had optimal technique. After 2 weeks, optimal technique (no errors) achieved in 0/7, 2/8 and 7/9 in the verbal counselling, augmented counselling and augmented counselling plus demonstration groups respectively (p=0.006).	The intervention was performed by one of the study investigators, who is a qualified pharmacist. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Basheti et al., 2008), Australia	To evaluate the feasibility, acceptability and effectiveness of a brief intervention about inhaler technique, delivered by community pharmacists.	Design: single-blind cluster randomised parallel group study. N: 97. Duration: 6 months.	Patients in the active group received inhaler technique training using augmented counselling and demonstration, repeated up to three times until the patient performed all steps correctly. An inhaler technique label was stuck on the inhaler device outlining the correct steps for using the inhaler device. The control group received usual care only.	Primary: peak flow variability (Min%Max). Secondary: inhaler technique, asthma severity.	Min%Max was not reported. Mean inhaler technique score improved significantly from baseline in both groups, but was significantly greater in the intervention group (for Accuhaler and Turbohaler combined, the mean change in score was 2.8 vs. 0.9, $p < 0.001$). Asthma severity was significantly reduced in the intervention group at 2, 3, and 6 months compared to the control group.	The intervention was performed by trained community pharmacists. Intervention performed in community pharmacies.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Giraud et al., 2011), France	To determine whether there is a link between inhaler technique (pMDI, Easi-Breathe or Autohaler), asthma control, and self-reported adherence.	Design: prospective observational study. N: 727. Duration: 1 month.	Inhaler technique training using verbal instruction and written instructions in the form of a sticker to attach to the inhaler device (average duration 6 minutes). There was no control group.	Primary: none stated. Secondary: inhaler technique, ACQ and Morisky assessment of adherence.	Immediately after community pharmacist training, optimal technique increased from 24% to 79% ($p<0.001$). At 1 month, mean ACQ improved from 1.8 to 1.4 $p<0.001$. Self-reported adherence improved from mean 1.4 (1.3) to 1.1, $p<0.001$. There were significantly greater improvements in ACQ and adherence n patients where inhaler technique improved.	No control group. The intervention was performed by community pharmacists. Intervention performed in community pharmacies.

3.3.3.7 Effects of interventions

See summary table of the effects of inhaler technique training on asthma control (**Table 2**) and Characteristics of included studies (**Appendix 2**) for details.

The shortest study was a two-week pilot study aiming to determine the most effective method of teaching patients how to use inhaler devices (Basheti et al., 2005). The intervention was performed by the lead researcher, a pharmacist, and found that verbal education strategies based on reading the patient information leaflet to the patient, with our without emphasis on the most critical steps, failed to ensure that most patients achieved optimal technique (defined as performing all the steps correctly) using a Turbohaler device. However when this was accompanied by physical demonstration of correct inhaler technique, high rates of optimal inhaler technique was achieved, and was significantly better than verbal education only. This study clearly demonstrated the importance for healthcare professionals to demonstrate correct inhaler technique when teaching patients how to use their inhaler device, as visual stimuli appear to be more successful than verbal education. The research group followed this study with a six-month single-blind cluster randomised parallel group study involving 31 community pharmacists, of whom 16 had received training on correct inhaler technique (Basheti et al., 2008). 97 patients prescribed a Turbohaler or Accuhaler device were randomised to receive intensive inhaler education with physical demonstration of correct inhaler technique from the trained pharmacists, at regular intervals and written instructions in the form of instruction stickers for inhalers, or to usual care from untrained pharmacists. Improvement in inhaler technique was significantly greater following intensive inhaler education, and was maintained over the six-month duration of the study. This was associated with a significant reduction in the proportion of patients with severe asthma, based on the National Asthma Council Australia criteria at 2-, 3-, and 6-months, and a significant correlation with improvement in peak flow variability. This study is of critical importance to pharmacy practice as it demonstrates that if the only intervention performed by pharmacists is to optimise inhaler technique, a significant improvement in asthma control can be produced. However, whilst optimal inhaler technique was promoted and maintained at frequent intervals in the initial stages of the study

(at baseline, one month, two months and three months), there was a small reduction in inhaler technique scores between three and six months where inhaler technique education was not reinforced. This demonstrates that inhaler technique should be checked at regular intervals, probably more frequently than every three months, even in patients who have taken inhaled medicines for long periods and have previously demonstrated good inhaler technique.

A limitation of the two studies by Basheti *et al*, was that there was no objective measure of inspiratory flow through the inhaler devices, which is known to be an important factor in ensuring an emitted dose with particles at the size required to deposit in the central and peripheral airways (Basheti et al., 2008, Basheti et al., 2005). This was addressed in two identical studies, one in a hospital outpatient department (Al-Showair et al., 2007), and one in community pharmacies (Ammari and Chrystyn, 2013). In these studies, patients using pMDI devices with an excessively fast peak IFR, which is known to significantly reduce lung deposition (Newman et al., 1995), were randomised to receive either verbal counselling alone or verbal counselling and training using a 2Tone Trainer whistle. Both studies included a control group of patients with correct inhaler technique and inspiratory flow through pMDIs. The 2Tone Trainer (Canday Medical Ltd, UK) is a pMDI shaped device that will whistle with a mono-tone when a person inhales through it at the optimal IFR, but will whistle with two-tones if a person inhales too fast through the device. In both studies, verbal counselling with or without provision of the 2Tone Trainer was associated with a significant reduction in peak IFR from too fast to the optimal rate for using pMDI, and this was associated with improvements in asthma quality of life using AQLQ (Al-Showair et al., 2007, Ammari and Chrystyn, 2013). There was no significant change in IFR or quality of life in patients in the control groups, demonstrating a real effect of education strategies on inspiratory flow and quality of life.

The results of these comparative studies have been replicated in uncontrolled prospective studies where all patients received inhaler technique training by either a nurse who provided education and demonstration of correct inhaler technique (Alamoudi, 2003) or community pharmacist who provided verbal and written instructions in the form of instruction stickers for inhalers (Giraud et al.,

2011). These larger studies have demonstrated significant improvements in inhaler technique associated with improvements in lung function (Alamoudi, 2003), asthma control measured using ACQ and adherence (Giraud et al., 2011).

In summary, these studies have demonstrated that inhaler technique can be improved with physical demonstration of correct inhaler technique. However, with the exception of one 6-month study, these studies were of short duration and so cannot provide evidence that patients can maintain optimal inhaler technique. In fact, the longest study showed small reductions in inhaler technique score towards the end of the 6-month study period, which may reflect patients falling back into bad habits of forgetting correct inhaler technique. A major limitation that this literature review identified was that few studies with control arms have been published, and data on widely recognised and validated asthma outcome measures were lacking. A further limitation was that only two studies (Al-Showair et al., 2007, Basheti et al., 2008) reported sample size calculations to demonstrate whether they were powered to demonstrate a significant benefit of inhaler technique training. Consequently it is unclear whether the remaining four studies were powered for the outcomes being tested.

3.3.4 The effect of interventions to improve adherence to inhaled corticosteroids on asthma control

3.3.4.1 Results of the search

After screening of study titles and abstracts, and removal of duplicates, 49 full-text articles were retrieved for consideration for review, and six were found to meet the eligibility criteria (see **Figure 3**).

3.3.4.2 Included studies

See Characteristics of included studies (**Appendix 3**) for details. Six studies met the inclusion criteria for the literature review (Bender et al., 2010, Gamble et al., 2011, Garcia-Cardenas et al., 2013, Janson et al., 2009, Strandbygaard et al., 2010, Williams et al., 2010).

3.3.4.3 Excluded studies

Of the remaining studies that were excluded from the literature review, nine were cross-sectional studies (Axelsson et al., 2009, Baddar et al., 2014, Bolman et al., 2011, Gamble et al., 2009, Hyland et al., 2012, Ivanova et al., 2008, Roy et al., 2011, Takemura et al., 2010, Moldrup et al., 2010), three were non-interventional studies (Clark et al., 2012, Williams et al., 2011, Wojtczak et al., 2012), three were uncontrolled observational studies (Giraud et al., 2011, Park et al., 2010, Sofianou et al., 2013), one was an audit (Murphy et al., 2012b), and one was a systematic review in asthma patients (Moullec et al., 2012).

26 other papers were excluded for various reasons including 15 that did not meet literature review inclusion criteria (Apter et al., 2011, Axelsson et al., 2013, Axelsson et al., 2011, Clerisme-Beaty et al., 2011, Douglass et al., 2012, Emilsson et al., 2011, Kang et al., 2013, Krauskopf et al., 2013, Lim et al., 2010, Mora et al., 2011, Ponieman et al., 2009, Santos et al., 2010, Shams and Fineman, 2014, Vaidya et al., 2013, Patel et al., 2013), five were review articles (Chan et al., 2013, Donaldson et al., 2013, Heaney and Horne, 2012, Horne, 2011, Roller and Gowan, 2013), two were study protocols (DiBello et al., 2013, To et al., 2013), one was a report of practice (Boise, 2014), one was a conference abstract (Engelkes et al., 2013), one was a letter (McNicholl and Heaney, 2013), and one was systematic review in a variety of long-term conditions (Haynes et al., 2008).

3.3.4.4 Interventions

See summary table of interventions to improve adherence to ICS on asthma control (**Table 3**) and Characteristics of included studies (**Appendix 3**) for details.

All the included studies were randomised trials. The interventions ranged from automated telephone calls (Bender et al., 2010) or text reminders (Strandbygaard et al., 2010), to intensive educational or motivational strategies that were performed by nurses in two studies (Gamble et al., 2011, Janson et al., 2009), GPs in one (Williams et al., 2010), and community pharmacists in a final study (Garcia-Cardenas et al., 2013). Adherence measures varied between electronic monitors in two studies (Bender et al., 2010, Janson et al., 2009),

prescription records in two studies (Gamble et al., 2011, Williams et al., 2010), review of inhaler dose counter in another (Strandbygaard et al., 2010), and use of the Morisky scale in a final study (Garcia-Cardenas et al., 2013). The varied study design and adherence measures make comparison between individual studies difficult.

3.3.4.5 Primary outcomes

See summary table of complex pharmacist interventions on asthma control (**Table 3**) and Characteristics of included studies (**Appendix 3**) for details.

Only three of the six included studies reported adherence as the primary outcome measure (Gamble et al., 2011, Strandbygaard et al., 2010, Williams et al., 2010), whilst two did not specify any primary outcome measures (Bender et al., 2010, Janson et al., 2009), and one reported ACQ as the primary outcome measure (Garcia-Cardenas et al., 2013). Asthma outcome measures incorporated a measure of asthma control (ACT, ACQ or perceived control of asthma questionnaires) in five studies (Bender et al., 2010, Gamble et al., 2011, Garcia-Cardenas et al., 2013, Janson et al., 2009, Strandbygaard et al., 2010), quality of life in four studies (Bender et al., 2010, Gamble et al., 2011, Janson et al., 2009, Strandbygaard et al., 2010), lung function in three studies (Gamble et al., 2011, Janson et al., 2009, Strandbygaard et al., 2010) and exacerbations in two studies (Gamble et al., 2011, Williams et al., 2010).

3.3.4.6 Risk of bias

The assessment and justification of the risk of bias for each of the included studies is presented in the Characteristics of included studies (**Appendix 3**). Three studies were judged to have low or unclear risk of bias for all domains (Bender et al., 2010, Gamble et al., 2011, Janson et al., 2009). All of the included studies were assessed to have low or unclear risk of selection bias, but two studies were judged to have high risks of bias due to performance and/or detection bias (Garcia-Cardenas et al., 2013, Strandbygaard et al., 2010), attrition bias (Williams et al., 2010), or reporting bias (Garcia-Cardenas et al., 2013).

Table 3. Brief summary of the effect of interventions to improve adherence to inhaled corticosteroids on asthma control

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Bender et al., 2010), USA	To examine the effectiveness of an interactive voice response intervention on adherence to controller medications	Design: randomised controlled trial. N: 50. Duration: 10 weeks.	5-minute interactive voice response telephone call (repeated once or twice at 1-month intervals depending on asthma control), which comprised core educational messages, encouraged filling of ICS prescriptions and to increase communication with their physician. The control group received no telephone calls.	Primary: not specified, but assumed to be adherence to controller medications. Secondary: ACT, AQLQ	Adherence over 10 weeks was 32% higher in the intervention arm than in the control group (mean 64.5% vs. 49.1%, p=0.003). No significant change in ACT or AQLQ.	Participants recruited from a tertiary care centre. Adherence measured using electronic tracking device on pMDI or Accuhaler, or by weighing Turbohaler.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Gamble et al., 2011), Belfast	To determine whether identified non-adherence to ICS/LABA inhalers in difficult asthma, could be improved using (i) a simple concordance interview and (ii) a menu driven psycho-educational intervention strategy, with better asthma outcomes.	Design: sequential 2-stage study. Phase 1 was an observational study; Phase 2 was a prospective single blind randomised controlled trial. N: phase 1: 83; phase 2: 20. Duration: phase 1: 9 months; phase 2: 12 months.	Phase 1: patient concordance consultation, resulting in an agreed treatment plan to address poor adherence. Phase 2: control vs. individualised psycho-educational nurse-led menu intervention to improve adherence	Primary: change in adherence to ICS/LABA. Secondary: daily ICS dose, use of OCS rescue courses, SABA use, hospital admissions, lung function, ACQ, AQLQ.	Phase 1: 31 of 83 non-adherent patients (37%) significantly improved adherence after concordance interview (in these 31 patients adherence increased from 37.3% to 88.5%). This was associated with a significant ICS dose reduction, fewer OCS rescue courses and hospital admissions. Phase 2: Greater improvement in adherence in the intervention group (37.6% to 61.9%), compared to the control group (31.7% to 28.8%); p=0.01. No effect on ACQ, daily ICS dose, AQLQ, use of OCS rescue courses, SABA use, hospital admissions, or lung function.	Intervention was performed in hospital difficult asthma clinic. Adherence as measured using prescription refill records.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Garcia-Cardenas et al., 2013), Spain	To evaluate the effect of a pharmacist intervention on asthma control	Design: cluster randomised trial. N: 346. Duration: 6 months.	Protocol-based intervention addressing individual needs related to asthma control, inhaler technique and adherence. The control group received usual care only.	Primary: ACQ Secondary: inhaler technique, adherence.	Adherence increased in the intervention (from 38.2% to 60.8%, p<0.001) and control groups (from 39.3% to 55.3%, p<0.001). The proportion of patients who were adherent at 6 months was significantly higher in the intervention group than in the control group (78.5% vs. 52.0%, p < 0.001). Significant improvement in ACQ in the intervention group (-0.66, p<0.001), but not in the control group (-0.15 (p value not reported).	Intervention performed in community pharmacies. Adherence was assessed using the 4-item Morisky-Green-Levine scale.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Janson et al., 2009), USA	To examine the effect of self-management education on adherence to ICS and markers of asthma control.	Design: randomised controlled trial. N: 95. Duration: 24 weeks.	Individualised self-management education (a 30 minute intervention, comprising provision of asthma information, assessment, inhaler technique education and asthma action plan, and trigger avoidance), plus self-monitoring of symptoms and PEF. The control group received usual care of self-monitoring alone.	Primary: not specified, but assumed to be adherence to ICS. Secondary: perceived control of asthma, lung function, quality of life.	No significant different in mean ICS adherence between the intervention and usual care groups (82% and 80% respectively at baseline, and 77% and 73% at 24 weeks). At 24 weeks, the intervention group maintained 3-fold greater odds of >60% adherence to ICS vs. control. Significant improvement in perceived asthma control in the intervention vs. control group. No significant difference in quality of life or lung function between the 2 groups.	Intervention performed in private and public community clinics. Adherence was measured using an electronic medication monitor attached to pMDIs.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Strandbygaard et al., 2010), Denmark	To examine the impact of daily text message reminders on adherence to asthma treatment	Design: randomised prospective study. N: 26. Duration: 12 weeks.	Daily SMS reminder (at 10am) on their mobile phone to take their asthma medication from weeks 4 to 12. The control group received no SMS reminders.	Primary: mean adherence rate to ICS/LABA. Secondary: ACQ, mini-AQLQ, exhaled nitric oxide, lung function, airway responsiveness.	Adherence improved in the intervention group and reduced in the control group; at 12 weeks the absolute difference in mean adherence rate was 17.8%, p=0.019. No difference between the two groups in ACQ, mini-AQLQ, exhaled nitric oxide, lung function or airway responsiveness.	Participants recruited from advertisements in free local newspapers. Adherence measured using ICS/LABA dose counter on Accuhaler device.

Citation, Country	Purpose of study	Study description	Interventions	Outcomes measures	Key findings	Comments
(Williams et al., 2010), USA	To assess the effect of supplying patient adherence information to primary care providers.	Design: cluster-randomised trial. N: 2698. Duration: 12 months.	Use of electronic prescription software to view ICS adherence, education for medical staff on non-confrontational approaches to discussing adherence, and include ways to identify barriers to taking medication, tips to help patients remember to take their medication, and methods to promote self-efficacy. The control group had no access to electronic prescription software.	Primary: ICS adherence over the last 3 months of the study. Secondary: emergency room visits, hospital admissions, OCS use.	No significant difference in mean ICS adherence at baseline (25.6% and 27.7%, p=0.21) or at 12-months (21.3% and 23.3%, p=0.553). Patients with stable or improved adherence had lower rates of emergency room visits and required fewer courses of OCS, but there was no effect on hospital admissions.	Intervention was performed in primary care practices, and provided by GPs. Adherence was measured using GP prescribing and pharmacy claims data.

3.3.4.7 Effects of interventions

See summary table of interventions to improve adherence to ICS on asthma control (**Table 3**) and Characteristics of included studies (**Appendix 3**) for details.

The two shortest studies of 10 - 12 weeks duration involved automated SMS text reminders to patients to take their ICS (Strandbygaard et al., 2010), or interactive voice response telephone calls to provide patient education and provide reminders to collect prescriptions (Bender et al., 2010). These two studies recruited small patient populations (26 and 50, respectively) and provide limited data relevant to cohorts of patients with severe asthma, due to either not reporting any baseline demographic data (Bender et al., 2010), or because the recruited sample population had a high proportion of patients who either had only mild (31%) or moderate (62.5%) asthma, or who were not prescribed any ICS at baseline (65.3%) (Strandbygaard et al., 2010). Consequently, whilst there was an increase in adherence associated with automated telephone calls or SMS text reminders, this was not associated in an improvement in asthma control or quality of life (Bender et al., 2010, Strandbygaard et al., 2010). It may be that a combination of a small population and short study duration may have resulted in the study being underpowered to detect any significant impact on important asthma outcomes associated with the improvement in adherence. However the fact that many patients had only mild to moderate symptoms and did not require regular treatment at baseline in one study (Strandbygaard et al., 2010) may have prevented significant improvements in asthma outcomes to be achieved in a relatively well controlled sample population.

Williams *et al* (2010), performed a large cluster-randomised trial that incorporated an educational intervention targeted to patients where poor adherence was identified using electronic prescription software (Williams et al., 2010). Adherence was poor throughout the study and overall it was not significantly affected by the intervention, but this was thought to be due to poor uptake of the intervention by GPs in the intervention group. This is supported by the observation that where the intervention was performed, a significant improvement in adherence was achieved compared to patients in the control group or where the intervention was not performed. Furthermore, in these

patients, the improvement in adherence was associated with reduced asthma exacerbations in terms of use of reduced OCS and emergency department visits, although not in terms of asthma-related hospitalisations.

Three studies employed complex educational and motivational strategies in order to improve adherence, two of which were performed by nurses in primary (Janson et al., 2009) or secondary care (Gamble et al., 2011), and one by community pharmacists (Garcia-Cardenas et al., 2013). Adherence was significantly improved over six to 12 months in two studies when measured using GP prescription data (Gamble et al., 2011), or patient self-reporting using the Morisky scale (Garcia-Cardenas et al., 2013), but this was associated with an improvement in asthma control (measured using ACQ) in only the latter study (Garcia-Cardenas et al., 2013). It is likely that the Gamble study failed to demonstrate a significant impact on asthma control, despite recruiting patients with difficult asthma (defined as at persistent symptoms of asthma despite treatment at BTS/SIGN step 4/5, and an ACQ >3.0) and following them up for a long duration, because only 20 patients were recruited and so the study may have been under powered (Gamble et al., 2011). In contrast to these two studies, Janson *et al* (2009) reported that overall adherence was not improved compared to control, when measured using electronic monitors attached to inhaler devices (Janson et al., 2009). Whilst mean adherence was noted to fall in both groups, it was found to be more likely to be maintained in patients in the intervention group, and consequently significantly more patients had a greater than 60% adherence to ICS in the intervention, than in the control group. This was associated with a significant improvement in perceived asthma control, quality of life and reduced use of SABA.

In summary, despite the varied study designs, interventions and adherence measures, these studies have frequently found that interventions aimed to improve adherence are successful and generally improve asthma outcomes. Studies that have not replicated these findings, have often either recruited inappropriate patients that have only mild asthma and/or required no asthma medication prior to the study, recruited only a small sample population are were likely to be underpowered, or the intervention was not consistently performed. Consequently, there is good evidence highlighting the importance of identifying

and addressing medication adherence concerns in patients with difficult asthma.

3.4 Summary

This literature review has examined the role of complex interventions provided by pharmacists in the management of asthma, and the importance of optimising inhaler technique and adherence in order to improve asthma control.

Whilst there is some evidence that complex interventions provided by pharmacists may improve asthma outcomes, there remain a number of gaps in the literature. These studies have all been based within community pharmacies, and often recruited a varied cross-section of asthma patients, with some well controlled and some who had uncontrolled asthma. There are currently no published randomised controlled studies examining asthma management by hospital pharmacists, nor are there any published randomised controlled studies examining the management of difficult asthma by pharmacists.

This gap in the literature confirms that the research study presented in this thesis is the first to investigate the effects of a redesigned pharmaceutical pathway across the primary and secondary care interface in patients with difficult asthma.

4 Methodology

4.1 Reflections on different research methods

The design of any research study should involve due consideration of a variety of different research methods to ensure that the most suitable approach is used to test the hypothesis under investigation. Research designs may be broadly classified as either survey, observational or experimental, and each was considered for this study.

Survey methods are used to measure certain phenomena, such as events or behaviours, in the population of interest (Bowling, 2002). However cross-sectional surveys are most commonly used to determine prevalence and to identify potential associations between an exposure or intervention and a possible outcome. These surveys are consequently descriptive and since data are collected at fixed points in time, they cannot test hypotheses, and further studies are usually required to confirm associations (Bowling, 2002, Campbell and Machin, 1999, Clancy, 2002, Mann, 2003). Alternatively, analytical longitudinal surveys may be used to analyse data at several points in time, which can suggest the direction of cause and effect associations, but again further studies would be required to confirm associations (Bowling, 2002). Therefore survey methods were not considered an appropriate research method since they would not have allowed the prospective determination of the extent of the impact of pharmacist interventions in a relatively small study.

Observational studies, such as cohort and case-control studies are often used when no interventions are made, or when randomised controlled experimental studies cannot be used. In these studies, the intervention is not controlled by the investigator, but a comparison is made between people with or without the disease for the outcome under investigation, allowing the extent of a causal relationship to be determined (Clancy, 2002).

The starting point for case-control studies is with the identification of cases comprising people with the disease or condition of interest, and then these are matched with controls comprising people without that disease or condition. The cases and controls are then compared to determine the potential relationship of a risk factor or past exposures on the disease or condition of interest (Campbell

and Machin, 1999, Clancy, 2002, Greenhalgh, 2006, Mann, 2003, Bowling, 2002). Case-control studies have the advantage that they are relatively inexpensive to perform as they are often quick and allow the assessment of multiple exposures (Clancy, 2002, Mann, 2003). However limitations in these studies include difficulties in identifying controls that are suitably matched and identical to cases and often require large number of participants to prevent selection bias, recall bias where cases suffering from a disease may be more likely to recall exposures to risk factors than controls, and measurement bias from the investigator if they know the outcome (Campbell and Machin, 1999, Clancy, 2002, Mann, 2003, Bowling, 2002). Consequently a case-control study was thought not to be appropriate for this research study, which examines the effect of an active intervention on, rather than investigating possible causes of, an outcome that is only appropriate for patients with asthma. Additionally it may be unlikely that a retrospective case-control study would allow analysis of all potential data pertinent to an asthma research study since many types of possible outcome test, such as quality of life measures, are not investigated in routine management.

A cohort study was considered a potentially appropriate observational research design as this method can be used to follow up two groups of patients prospectively, one of whom has experienced an exposure or an intervention, and determine the effect on a particular disease or outcome. This type of observational study most closely resembles randomised controlled experimental studies, except that the investigator does not control the allocation to the exposure or intervention (Campbell and Machin, 1999, Clancy, 2002, Greenhalgh, 2006, Mann, 2003, Bowling, 2002). However cohort studies are most commonly used to study the incidence or prognosis of disease, or to investigate aetiological factors (Campbell and Machin, 1999, Mann, 2003, Greenhalgh, 2006). Retrospective cohort study designs may be appropriate where it is unethical to examine the effect of an intervention or exposure in an experimental study, such as the exposure to an environmental toxin and are generally simpler to perform than experimental studies.

It was considered that a prospective cohort study could have been designed for this research study, with one cohort undergoing usual care and a second cohort

undergoing the intervention from a pharmacist and the outcomes observed. However as the research aims and objectives were clearly indicating that the effects of an active intervention by pharmacists were going to be assessed, an experimental design was considered more appropriate than a cohort study, and was not thought to be ethically problematic. A retrospective cohort study was also considered, as this could look at the impact of pharmacist interventions in one cohort of patients compared to a second cohort where no pharmacist intervention was made. However it was thought that this study design would be logistically difficult to perform, as it would be unlikely that sufficient data on relevant outcome measures would be available to study the impact of pharmacist interventions, and matching the two groups of patients could be difficult.

Experimental studies describe research methods comprising at least two differently treated identical groups, where the experimental group are exposed to an intervention under investigation, whilst a second control group is not exposed, and both groups are then followed up under tightly controlled and defined conditions (Bowling, 2002, Clancy, 2002). The randomised controlled trial is considered to be the gold standard experimental study design, where patients should be randomly allocated to either the experimental or control group in order to prevent bias and differences developing between the two groups (Greenhalgh, 2006, Kendall, 2003). Furthermore, experimental studies are considered to be the only research design that can yield causal results and allow powerful statistical manipulation of data (Bowling, 2002). However it is often hard to design experiments that represent the overall general patient population and thus produce data that are valid in the ‘real world’, and such studies are often expensive in terms of time and money (Bowling, 2002, Greenhalgh, 2006). Furthermore, it is also considered that randomised controlled trials may be either (i) unnecessary if the effect of an intervention is likely to be dramatic or where there are previous studies demonstrating a definite effect; (ii) impractical if it would be unethical to recruit patients to the study, or where large numbers of patients would be required for the study due to infrequent outcomes under investigation; or (iii) inappropriate where an alternative study design is preferred, e.g. using a cohort study to investigate the prognosis of the disease (Clancy, 2002, Greenhalgh, 2006).

Consequently it was considered that an experimental study design should be used to investigate the impact of pharmacist interventions of asthma control in patients with difficult asthma, since this would allow the prospective data to be collected to quantify effect of the intervention compared to a control group that did not receive the intervention.

As the lead researcher was performing the interventions in the PI group, this meant that this study met the criteria for being action research, as it sought to generate new knowledge on the management of difficult asthma whilst simultaneously trying to change it (Bowling, 2002). There are concerns that such action research may affect the validity of the study because the researcher has a direct involvement with the study rather than being an objective outsider, and may introduce bias even subconsciously by subjectively misinterpreting data or making false assumptions. Conversely, action research may have advantages compared to independent research as the insider may be able to access and obtain data and information from patients more easily due to familiarity between the subjects of the study and the researcher (Asselin, 2003, Bowling, 2002).

4.2 Reflections on experimental study design for an interventional study

Prospective and retrospective data collection methods were considered when designing this study. Prospective studies have advantages over retrospective studies because they usually have fewer potential sources of bias and confounding than retrospective studies, and may be easier to ensure that all data are collected, particularly in this study where a number of outcomes were investigated, where data are not collected in routine practice. Consequently, this research study was designed as a prospective, randomised, open study.

Quantitative and qualitative methods for data analysis were considered, but qualitative methods requiring interviews and focus groups were discounted as these tend to focus on understanding the meanings that study participants might attach to their social world, rather than providing a measure of the extent of the effects of an intervention (Bowling, 2002). In this study examining the

effects of pharmacist interventions in the management of patients with difficult asthma, there is a lack of data whether or not this intervention is beneficial in this subgroup of asthma patients. Consequently, it was thought that the primary objective of this study should be to investigate the extent of this impact of pharmacist interventions on objective measures of asthma control and symptoms, rather than subjective assessments based on interview methods.

The simplest experimental studies analyse the effects of one single intervention compared to no intervention, and this is the format used in randomised controlled trials of a drug versus placebo (Craig et al., 2008). However interventional studies are frequently complex as the main intervention is frequently associated with other aspects that need to be considered. In this study, assessing the impact of pharmacist interventions in difficult asthma, there are a number of interventions that have been seen to be effective in the literature review (see **Chapter 3.3.1)**, including education about asthma, education about medication, self-management and trigger avoidance, and inhaler technique training. Each of these may have an impact on overall asthma symptoms and asthma control, and may impact both independently and inter-dependently, and is therefore described as a complex intervention (Craig et al., 2008). Additionally, since it is likely that individual patients will have different aspects of their asthma that require addressing, it is likely that the interventions made will vary from patient to patient. For example, some patients may require the intervention to concentrate on education about asthma self-management, whilst others may require additional training on correct inhaler technique. Overall, it is likely that each patient may undergo a number of varying interventions, since this has previously been demonstrated to improve adherence and asthma symptoms, when provided by doctors or nurses (Bailey et al., 1990, van Es et al., 2001, Put et al., 2003, Moullec et al., 2012). Further complexity to the intervention was introduced following initial pilot studies, which found that the involvement of community pharmacists to provide follow-up assessment and intervention was a necessity due to clinic capacity restrictions (see **Chapter 4.6**).

In the context of this study, which comprises a complex intervention, it is usually advisable to consider a randomised study design to prevent bias being

introduced into the study (Craig et al., 2008). However since an important outcome from the study was to understand whether the interventions have a positive impact on asthma control and asthma symptoms under real-life conditions and therefore whether a pharmacist-led asthma service should be provided, a pragmatic research study was designed. In contrast, clinical, explanatory studies rarely reflect routine practice and have very narrow patient selection criteria and require a very strict intervention, rather than as an intervention that differs from patient to patient (Roland and Torgerson, 1998).

The nature of the intervention precluded the study design from being blinded as it would be impossible to prevent the researcher from knowing which patients had undergone usual care and which had undergone the pharmacist intervention. This is because there was no practical way for the lead researcher to be blinded as he was also responsible for patient recruitment, randomisation, providing assessment questionnaires (e.g. ACQ, AQLQ(S)) to all participants, performing the baseline intervention to participants in the PI group, and performing the follow-up inhaler technique assessments in all participants. At the time of the study, there were no other pharmacists working in the study centre who met the criteria of advanced specialist pharmacist who could have performed the intervention in order to separate the roles of researcher and pharmacist.

As the interventional study had to be unblinded, it was important to institute a selection method to prevent patients being actively selected in a manner that could institute bias into the study. This was itself difficult, since the researcher was principally responsible for identifying suitable patients to be invited to participate in the study, in collaboration with the lead consultant in the difficult asthma clinic. A convenience sampling method was considered as a simple way to identify prospective patients for the study, because the primary setting for the study was in the local difficult asthma clinic, and would be easier than trying to randomly recruit potential patients from the local population. Convenience sampling methods may assist recruitment, allow easier monitoring, and are thought to achieve good response rates with low attrition rates (Bowling, 2002). However, since patients with alternative diagnoses such as COPD, bronchiectasis, or mild to moderate asthma were often booked into this clinic,

purposive criteria were applied before recruitment and randomisation (Bowling, 2002). Therefore, the investigator and clinical supervisor reviewed future clinic lists to ensure the suitability of individual patients for the study, as well as ensuring that they had a confirmed diagnosis of asthma, since significant numbers of patients attending difficult asthma clinics may have alternative diagnoses (Heaney et al., 2003, Barnes and Woolcock, 1998).

An unrestricted random allocation method, performed after each patient had provided written, informed consent to participate in the study, was also used to prevent bias in intervention allocations and to attempt to minimise differences between patients in the two intervention groups (Bowling, 2002). It was identified that there was an unavoidable risk of contamination of the control group as patients in both the intervention and usual care group would be reviewed within the same clinic, as the difficult asthma clinic was located on just one hospital site within the Trust. Furthermore, there are relatively few hospital Trusts in the UK that operate similar tertiary referral difficult asthma clinics, and very few that incorporate advanced clinical pharmacists into the difficult asthma service in the UK. In 2006, there were no difficult asthma clinics that had direct access to pharmacists in clinic (Roberts et al., 2006), and to my knowledge there is currently only one in the North of England, which was the study centre. This therefore prevented a multi-centre study design being used, which would have allowed for a cluster randomisation allocation method to be used and reduce the risk of contamination bias. However several study centres would have been required to allow each site to only recruit a small number of patients to reduce the risk of data from one cluster site dominating the overall outcome effects (Craig et al., 2008, Bowling, 2002), and this would not be achievable.

There were no practical or ethical reasons for discounting an unrestricted random allocation method in this study and patient recruitment was not anticipated to be a problem. Similarly it was not thought that patients might have strong preferences about their treatment allocation, which could affect patient recruitment. Consequently other experimental designs such as preference trials or randomised consent studies (Craig et al., 2008) were not considered as necessary.

A further potential problem with random allocation methods was due to the relatively small study population required to allow the study to be adequately powered to demonstrate a potential improvement in asthma control with pharmacist-led management of asthma. There was a risk that random allocation methods involving a small study population could result in a random imbalance in patient numbers in each group. Therefore, a random permuted blocks allocation method was used to ensure that approximately equal numbers of patients were assigned to each intervention arm (Campbell and Machin, 1999). Other allocation methods such as stratified randomisation and minimisation methods (Bowling, 2002) were discounted since they were not relevant to the study design.

4.2.1 Reflections on study settings

A number of settings for the study were considered, including being based within secondary care at the difficult asthma clinic at the hospital, or within primary care in community pharmacies or designated GP practices.

A study based in primary care may be more convenient for patients to attend, particularly if multiple study sites are identified in community pharmacies. However, as the study was designed to investigate the management of patients with difficult asthma, which usually takes place within secondary care, it was considered essential that the location of the pharmacist intervention should take place within this same setting. This would ensure that patients were treated equally apart from the intervention, because locating the pharmacist intervention in primary care may result in a design bias (Bowling, 2002).

An intervention solely delivered by pharmacists working within community pharmacies or GP practices could possibly result in an unintentional negative bias, if patients with difficult asthma think that these pharmacists may not have the expertise to manage their condition, which could have adversely affected recruitment rates, or affect patients' adherence to the intervention. One patient preference study reported that the majority of patients rated asthma services in community pharmacies as good to excellent (Naik-Panvelkar et al., 2012), but the opinions of patients with difficult asthma on pharmacist-led services is unknown. Alternatively patients could be more likely to report improvements in

asthma control and symptoms, especially if they know their pharmacist who is performing the intervention. This is an example of acquiescence bias (Bowling, 2002), and may be managed by using validated measures of asthma control and quality of life.

A final risk of setting the study in GP practices or community pharmacies is that it would be difficult for all GP practices and community pharmacies to be recruited as study sites for economical and logistical reasons, despite this approach potentially maximising patient recruitment. Consequently this approach would require a cluster sample of practices or pharmacies to be used as study sites, but this could incorporate risk associated with the location of the practices or pharmacies, as different socio-economic factors might affect asthma control, and could result in the sample population being unrepresentative of the overall population. However evidence about a link between socio-economic status and difficult asthma is limited and is variable across the UK (Heaney et al., 2010).

Setting the study in hospital would overcome problems associated with potential sampling biases as patients are referred from all GP practices in the local area and thus patients from all socio-economic backgrounds may be encountered. Patients with uncontrolled asthma in Leeds are referred to the local difficult asthma clinic, which allows easy identification of suitable participants for the study.

Therefore it was decided to conduct this study in the Leeds Difficult Asthma Clinic at Leeds General Infirmary, Leeds, West Yorkshire. The Leeds Teaching Hospitals NHS Trust serves a population of approximately 757,655 people (Office for National Statistics, 2013). This site was selected, as it has a difficult asthma clinic that reviews patients appropriate for this study, and is the employing organisation of the researcher and the clinical supervisor. The difficult asthma clinic operates on one day each week and has capacity for two consultants, one or two specialist registrars, one asthma nurse specialist and one pharmacist to review patients.

Setting the study in the difficult asthma clinic would allow interventions in two study groups to be performed in the same clinic setting, ensuring that both study groups would be treated equally. This would also allow for follow-up interventions in the pharmacist intervention group to be performed in the same clinic, ensuring a consistent approach to asthma management in the study. Similar pharmacist intervention studies, set in community pharmacies utilised regular follow-up interventions, such as at months 1, 3 and 6 to reinforce the baseline intervention (See **Chapter 3.3.1**) (Armour et al., 2007, Basheti et al., 2008, Charrois et al., 2004, Mangiapane et al., 2005, Mehuys et al., 2008). However, due to insufficient capacity within the clinic, it was not possible to perform additional routine follow-up visits in addition to baseline and end of study visits in the difficult asthma clinic. Therefore it was decided that follow-up reinforcement of baseline interventions could be performed by community pharmacists who provide the nationally commissioned t-MUR service (Department of Health, 2013) (see **Chapter 4.6**). The involvement of community pharmacists providing t-MUR follow-up of participants in this study was supported by the Chief Executive for Leeds, Bradford & Airedale, Calderdale & Kirklees Local Pharmaceutical Committees (now known as Community Pharmacy West Yorkshire) (see **Appendix 4**).

In order to ensure that community pharmacists had the knowledge and skills to undertake effective targeted asthma MURs, two evening educational sessions on asthma, the medical condition, its treatment and management were arranged with the Leeds, Bradford and Airedale Local Pharmaceutical Committee. Bradford and Airedale were encouraged to attend, particularly those working in areas with high admission rates due to asthma. Funding for these sessions were not available for community pharmacists outside this region, and so patients attending the difficult asthma clinic as a tertiary referral from outside this region were not recruited to the study.

The format to these educational sessions were broadly similar to sessions arranged in other interventional studies (Charrois et al., 2004, Basheti et al., 2008, Armour et al., 2007, Mehuys et al., 2008), comprising education of the pathophysiology, trigger factors and the pharmacological and non-pharmacological treatment of asthma, followed by education on the importance

of and method of teaching inhaler technique. In addition community pharmacists working in areas of Leeds and Bradford with high admission rates due to asthma were also encouraged to attend follow-up intensive educational sessions on inhaler education.

Inhaler technique training for community pharmacists at these educational sessions was provided by the lead investigator for this study, who has expertise on theoretical and practical aspects of inhaler technique (Capstick and Clifton, 2012). Education on asthma pathophysiology, trigger factors and the pharmacological and non-pharmacological treatment of asthma was provided by one of the local consultant respiratory physicians.

4.3 Study population

The study population comprised adult patients, aged 18 to 70 years, with a clinical diagnosis of asthma, and fulfilled the criteria for difficult asthma (see **Chapter 2.1.2**). The inclusion criteria was set to be broad in order to ensure that the research study would be inclusive and open to as many patients as possible, based on the fact that there are relatively fewer people with difficult asthma than mild to moderate asthma.

There is known to be a certain degree of diagnostic uncertainty with patients attending difficult asthma clinics, as many may have an alternate diagnosis (Barnes and Woolcock, 1998), or significant co-morbidities that contribute to their symptoms (Heaney et al., 2003). Therefore it was decided that all recruited patients must have a diagnosis of asthma confirmed by a consultant respiratory physician based on subjective and objective criteria, such as demonstration of airflow obstruction on spirometry (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). Patients with other co-morbidities that could contribute to their respiratory symptoms were excluded because other respiratory conditions such as bronchiectasis or COPD may not respond to an intervention focussed upon asthma education and treatment.

It was considered that this research study should attempt to recruit patients of all severities from mild to severe asthma. However many asthma patients will

remain well controlled and require limited intervention from healthcare professionals, and so it may be unlikely that an interventional study would achieve significant impact in people with well-controlled asthma. Indeed, some community pharmacy studies have targeted patients with mild to moderate asthma and have failed to demonstrate a significant impact on asthma control after pharmacist interventions comprising education, inhaler technique training and smoking cessation advice (Mehuys et al., 2008).

Consequently, it was decided that it was most appropriate to target patients who are labelled as having ‘difficult asthma’, defined by the BTS/SIGN asthma guidelines as persistent symptoms and/or frequent exacerbations despite treatment at step 4 or step 5 (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). It was thought appropriate to include only patients with difficult asthma despite previous studies that have failed to demonstrate a significant impact after intervention from community pharmacists in patients at high risk of asthma exacerbations (Charrois et al., 2006). This is because compliance with the intervention was poor in that study, and it is possible that the lack of specialist training, knowledge and skills of community pharmacists may have adversely affected the study.

A number of sampling methods to recruit patients were considered including selecting patients from within the difficult asthma clinic itself, during admission to hospital because of an exacerbation of asthma, or from GP practices. There is however no specific register of difficult asthma patients in primary or secondary care from which to identify potential suitable patients for the study. Additionally, advertising in the local newspaper for potential patients was not considered, as the cost of this was prohibitive.

Since the primary setting for the study was in the local difficult asthma clinic, recruitment from patients referred to the difficult asthma clinic had advantages over the other methods, as this provided an easily accessible cohort of patients thought to have difficult asthma. In addition to ease of recruitment, this would allow ease of monitoring and follow-up, and has been shown to have generally good response and retention rates within single clinic settings (Bowling, 2002).

Hospital admissions allowed another source for identifying suitable patients, but would require screening of all admissions to respiratory and medical admission wards to identify patients who potentially met the inclusion criteria. This was thought to be too labour intensive to be a practical method, and suitable patients tended to be referred to the difficult asthma clinic anyway, and consequently the screening of hospital admissions could duplicate the effort to identify the same patients.

Screening of patients registered with GP practices was considered a method that could potentially highlight large numbers of patients that could be invited for the study, but it was decided that it was impossible to screen all asthma patients in each of the 112 GP practices within the three Leeds Clinical Commissioning Groups. A cluster sampling method (Bowling, 2002) selecting specific GP practices would have been required to screen for suitable patients, but this would have risked creating sampling errors if practices were not representative of the general patient population. In addition, some GP practices may have been better at managing asthma than others, so it could be harder to demonstrate a positive response to the intervention in this scenario. Similarly, if the majority of patients are recruited from GP practices where asthma is not managed so well, there could be a potential for a greater impact of the intervention in the sample than would be expected for the whole population. Consequently, it was decided that the most appropriate sampling method for the study was to identify patients from the hospital difficult asthma clinic.

4.3.1 Sample size

On the 7-point scale of the ACQ, a change in score of 0.5 is the smallest that can be considered clinically important. In the original validation study, the ACQ was able to detect a change in asthma control with a mean change (± standard deviation (SD)) of 0.73 ± 0.54 (Juniper et al., 1999b, Juniper et al., 2000).

A sample size calculation can be based on the ability to detect a difference of 0.5 in the mean ACQ score, assuming a SD of 0.54. Therefore for a power of 80% and a two-tailed significance level of 5%, the required study population is 38 patients. However, allowing for an attrition rate of 25%, observed in other

studies of Pharmacist intervention in asthma patients, the sample size required for this study is 52 patients.

This is based on a Comparison of means (unpaired data) sample size calculation:

$$m = \frac{2(Z_\alpha + Z_{2\beta})^2 \sigma^2}{\delta^2}$$

Where:

$m =$	The approximate number of patients per group
$\sigma =$	The standard deviation
$\delta =$	The difference in mean response between the intervention and control groups
$2(Z_\alpha + Z_{2\beta})^2$	A function based on the study power of 80% (=7.849)

Therefore:

$$m = \frac{2 \times 7.849 \times 0.54^2}{0.5^2}$$

Therefore m = 19 patients per group.

4.4 Study method

The study was designed as a pragmatic six-month, prospective, randomised, open trial in which patients were randomised to pharmacist intervention (PI), or usual care (UC). The study procedure is summarised in **Figure 4**.

The inclusion criteria included patients, aged 18 to 70 years, with a clinical diagnosis of asthma, and fulfil the criteria for difficult asthma, who were able to speak, read and write in English, and were eligible for a MUR. Patients were excluded if they were not responsible for taking their own medications, or failed to provide written informed consent.

Screening future clinic lists and past clinic letters at the Leeds difficult asthma clinic identified patients for inclusion in the study. This was performed by the

investigator and reviewed by the clinical supervisor to ensure that potential patients had a confirmed diagnosis of asthma and met the criteria for difficult asthma. At least 2 weeks prior to their scheduled Difficult Asthma clinic appointment, a letter was posted to each patient who met these criteria inviting him or her to participate in the study. This letter was addressed from the Lead Consultant, introducing and describing the study and a copy of the patient information sheet was included with it (see **Appendix 5**).

On the scheduled date of each screen patient's appointment at the difficult asthma clinic, their medical notes were reviewed and patient questioned to ensure that they met the full study inclusion criteria, and written informed consent (**Appendix 6**) was obtained if they agreed to enrol in the study.

Patients were randomly allocated to one of two intervention arms. The first was the UC group, where patients received the 'usual' standard asthma review in clinic from a consultant, specialist registrar, or specialist respiratory nurse in line with the 'usual' standard difficult asthma clinic procedures. The second was the PI group, where patients received an asthma review from an advanced clinical pharmacist in clinic, comprising education on asthma and medication, inhaler technique training in addition to the 'usual' standard asthma review.

4.4.1 Intervention group

A protocol for independent practice was developed to guide the investigator in managing patients with difficult asthma (see **Appendix 7**). This was based on observation of the methods used by senior clinicians, as well as on the content of other educational intervention studies identified in the literature review.

The intervention provided by the advanced clinical pharmacist, an autonomous independent prescriber, in the difficult asthma clinic comprised:

1. Patient education on asthma pathology and medication, and self-management, including the use and provision of a peak flow meter and Asthma Action Plan where necessary. This has formed an integral component of most pharmacist interventional studies, as described in the literature review (**Chapter 3.3.1**), and so formed an similarly essential component of the intervention (Gibson et al., 2002b, British Thoracic Society

and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014, Armour et al., 2007, Charrois et al., 2006, Mangiapane et al., 2005, Mehuys et al., 2008).

2. Inhaler technique assessment and optimisation using a structured assessment, using a ‘‘show and tell’’ inhaler technique training method (Basheti et al., 2008), where inhaled technique is observed and assessed using a checklist (**Appendix 8**) up to a maximum of three times for each device. In addition, inspiratory flow for different devices was determined using an In-Check DIAL flow meter (Clement Clarke, UK) to ensure that patients used the correct inhalation speeds to use their inhaler devices optimally (Capstick and Clifton, 2012).
3. Asthma assessment and review, which was based on components described in asthma guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014) and SIMPLES approach for primary care physicians (Ryan et al., 2013):
    a. Assessment of asthma control
    b. Where appropriate, review of: past asthma history (e.g. exacerbation frequency requiring OCS use or hospital admission), associated medical conditions that may impact on asthma control (e.g. symptoms of gastro-oesophageal reflux disease, rhinitis), family history.
    c. Adherence assessment, using on non-confrontation questioning of the patient (Gamble et al., 2011, Gamble et al., 2009).
    d. Review of aggravating factors, such as allergies, lifestyle (e.g. weight, diet and nutrition, smoking status), and housing condition [e.g. presence of mould or damp, pets, or dust).
    e. Medication review, ensuring their prescription is in line with the BTS/SIGN 2012 Guidelines on the management of asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014).

All patients in the PI group were referred by telephone and in writing (see referral form, **Appendix 9)** for a t-MUR from their usual community pharmacist, to take place between weeks 4 to 8. All patients were followed up at 6 months.

4.4.2 Usual care group

Patients randomised to this group had routine management comprising a standard review from a Consultant Physician, Specialist Registrar or Asthma Nurse Specialist. Standard practice is to assess asthma control, compliance, inhaler technique, and aggravating factors, then step up or down therapy as appropriate. Patients in this group were excluded from having a t-MUR during the study. All patients were followed up at 6 months.

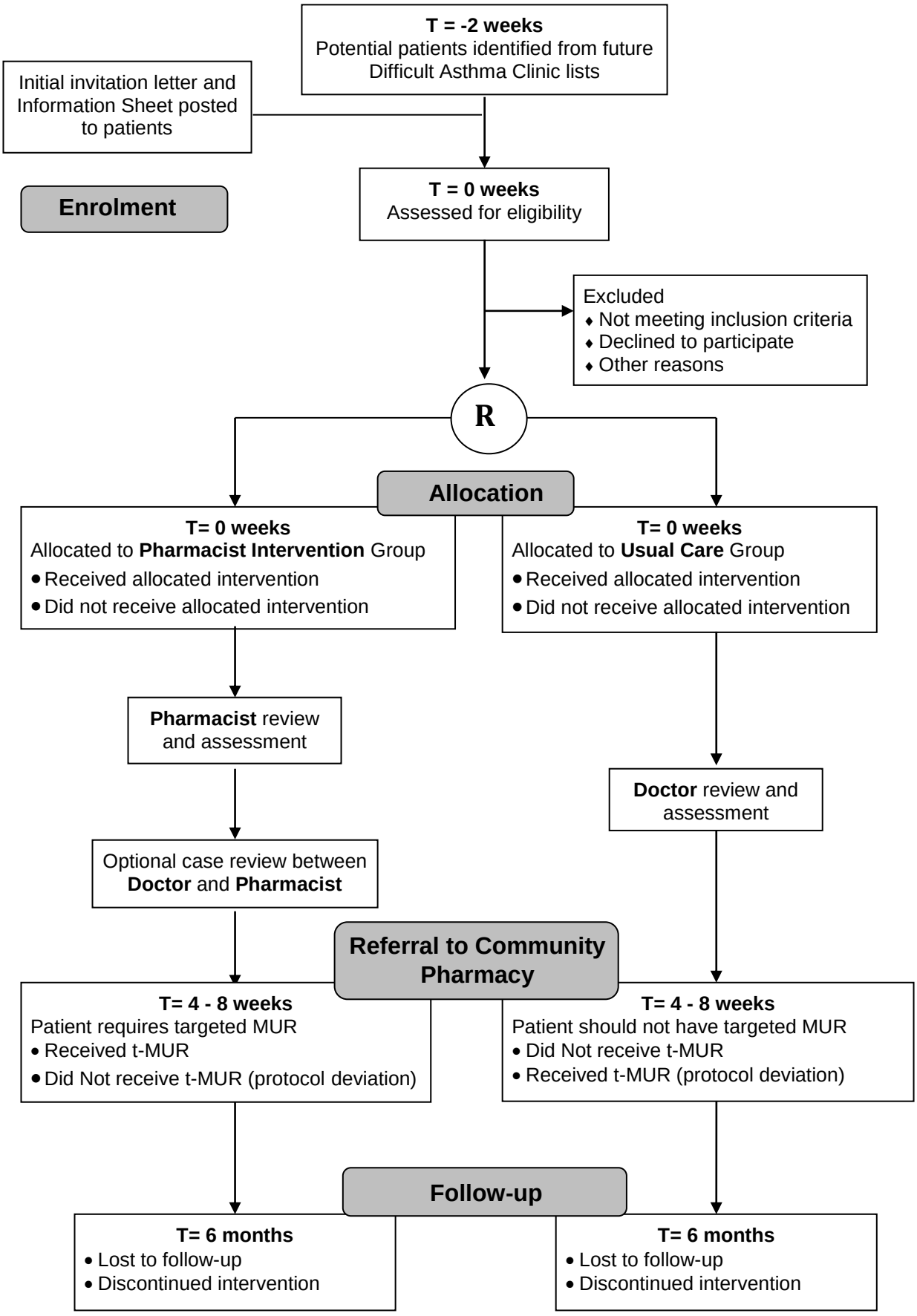


Figure 4. Study Procedure

Includes anticipated potential patient deviations from protocol.

4.5 Consultation review

Studies have demonstrated that the experience of patients' consultations were more likely to be positive when their physician listened to them carefully and demonstrated nonverbal attention, employed an interactive conversation style, and tailored individualised treatment plans, and may lead to a reduction in healthcare use and improvements in health outcomes (Clark et al., 2008, Stewart, 1995). Other studies have reported favourable outcomes and more honest answers when questions on adherence are phrased in a non-threatening manner (Horne and Weinman, 2002).

As a consequence, GINA recommend that the key components of effective asthma consultations include demonstrating a congenial demeanour, showing empathy and reassurance, engaging in interactive dialogue, giving encouragement and praise, giving appropriate personalised information, eliciting shared goals, and ending the consultation with feedback and review (Global Initiative for Asthma, 2014). It was essential therefore that the consultation style used by the researcher followed a similar format to these studies and guidelines, because this interventional study is largely based on education and training that is provided verbally.

Therefore a communication style based on the enhanced Calgary-Cambridge consultation model (Kurtz et al., 2003) was used. This aims to allow a rapport to develop between the investigator and patients and ensure that patients experienced a satisfactory approach to their consultation. This consultation model emphasises the importance of building a relationship with patients and to explore the patient's own perspective of their illness including their ideas, beliefs, concerns and expectations. This allows healthcare professionals to obtain the required information to perform a medical review, and then discuss findings and management options with patients.

Whilst the content of the consultation is discussed previously (**Chapter 2.3.3**), it was considered important that the format and consultation style had a specific objective to change patients' behaviours in order to improve their own self-management of their asthma and where necessary improve adherence to treatment. Traditional methods for improving adherence have focussed on

simplifying treatment regimens such as through the use of ICS/LABA combination inhalers, and ensuring that inhaler devices are prescribed that patients can use. However more recently, cognitive-based behaviour change techniques (CBCT) have been recommended for use by healthcare professionals to improve adherence.

It was therefore important to incorporate some of the CBCTs into the intervention in my study. However due to the complexities of behaviour change interventions and the time required to use these in an identical manner to published studies, only brief behaviour change interventions could be incorporated, but focussed on self-monitoring, identification and avoidance of asthma triggers, addressing erroneous views about asthma and its treatment. These interventions assist the development of a self-management plan (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014) and this combined with CBCT can help motivate patients to improve their asthma management and asthma control.

4.6 Feasibility and piloting

4.6.1 Feasibility of patient recruitment

In order to ensure that sufficient patients could be recruited to the study to be powered to demonstrate a positive impact of pharmacy interventions, a three-month audit using a self-reporting questionnaire design was performed to determine the number of patients likely to meet the inclusion criteria for MUR (Capstick et al., 2012). Over a 12-week period between November 2011 and February 2012, 237 patients were scheduled to attend the Leeds Difficult Asthma Clinic and 64 completed questionnaires (10 new referrals and 54 follow-up attendees), representing a 27% response rate.

50 patients reported that they used the same community pharmacist for at least the past 3 months, and 33 (66%) of these patients who would be eligible for a MUR had not received this service within the past 12 months. At the time of the audit approximately 70% of community pharmacies were registered with their Primary Care Trust to provide an MUR service, and consequently most of these

patients were likely to have attended community pharmacies that provided this service.

By assuming that the completion rates of the questionnaire would be equivalent to consent rates for participation in the study, it was thought possible that 36% of consenting patients (70% of 33/64 patients) attending the Leeds Difficult Asthma Clinic were likely to be eligible for a t-MUR as part of the study protocol, and attend a community pharmacy that provided a MUR service. As the audit took place over a 12-week period, this would equate to 3 patients per week who may be likely to consent to inclusion in the study and be eligible for and able to have a t-MUR. Due to the number required, it was thus anticipated that patients could potentially be recruited to the study over a 9 to 12 month period.

4.6.2 Pilot study

In order to ensure that the study intervention was viable, the researcher reviewed patients within the difficult asthma clinic according to the intervention protocol, and found that it was appropriate, achievable and acceptable to patients. However as mentioned above (**Chapter 4.2**), the initial study design comprising reinforcement follow-up visits was found to not be possible because the hospital difficult asthma clinic was limited such that there was insufficient capacity within the clinic to allow additional repeated follow-up outpatient visits. The initial study design plan specified that patients would return for review and reinforcement of education and inhaler technique training at regular intervals (after 1, 3 and 6 months) as previous community pharmacy-based interventional studies incorporated one to three follow up visits in between the baseline and final visits to reinforce the intervention and assess asthma outcomes (Armour et al., 2007, Basheti et al., 2008, Charrois et al., 2004, Mangiapane et al., 2005, Mehuys et al., 2008). As this was not possible alternative methods for providing reinforcement education and assessment were considered, and the role of community pharmacists providing the nationally commissioned t-MUR (Department of Health, 2013) was thought to be suitable to provide this role.

Whilst previous pharmacist intervention studies had used at two or three reinforcement interventions, patients are only allowed one MUR every 12 months (Department of Health, 2013). This caused concerns that interventions

made during the baseline consultation could not be reinforced by community pharmacists on a regular basis, but pragmatically it was thought that one reinforcement visit would more closely mimic NHS services than previous pharmacist intervention studies, and provide data more relevant for usual clinical practice.

All patients reviewed in this pilot stage were excluded from the main study.

4.7 Data Collection

The aim of this study was to determine the effects of a co-ordinated management strategy between primary and secondary care pharmacists on asthma control and quality of life in patients with difficult asthma. Therefore, as this study was designed as a pragmatic interventional study in a real-world setting, it was important that the outcome measures investigated were relevant for clinical practice, using measures that are meaningful and relevant for assessing asthma symptoms and control in individual patients, and therefore allowing the results to be interpreted into routine practice.

Additionally, it was also important for outcome measures to be similar to those employed in other pharmacist intervention studies, so that the results of this study could be compared to previous research.

Outcome measures selected for the proposed study were based on the American Thoracic Society (ATS) / European Respiratory Society (ERS) statement on standardising endpoints for clinical asthma trials and clinical practice (Reddel et al., 2009). The primary endpoint in this study was the impact on asthma control from the management of difficult asthma by a hospital advanced clinical pharmacist and a community pharmacist, and so it was important that validated and approved measures of asthma control were employed. The ATS and ERS recommend composite scores to measure asthma control and quality of life, as well as lung function and symptom-based outcome measures such as the number of symptom-free days, reliever use and exacerbation history (Reddel et al., 2009).

A data collection form was designed to collect data on the outcome measures and where data were collected using additional questionnaires, a tick box was included to remind the investigator to ensure all questionnaires were completed and collected (see **Appendix 10**).

Whilst most of the data were collected by the investigator, data for patients undergoing usual care was collected by clinic nurses and doctors who were reviewing the patient. Therefore, to ensure complete data collection, the form was designed to highlight which sections were to be completed by non-researcher staff managing patients in the usual care group.

4.8 Outcome Measures

Due to limited time and staff resources, it was decided that the study design should be simple for both the research process and patients. There was limited time available during each patient's clinic appointment to teach patients how to complete patient diaries that are frequently used in clinical trials to assess daily asthma symptoms and control. Instead it was decided to collect data at baseline and at six-months, and to collect indirect measures of asthma control such as corticosteroid use and hospital admissions, which are accepted outcome measures for asthma control (Reddel et al., 2009).

A six-month follow-up period was chosen since this is thought to be the minimum duration required to identify outcomes such as unscheduled use of secondary health care including hospital admissions and attendance in the A&E department (Reddel et al., 2009). This interval was also desirable on a practical basis since it prevented patients having to attend the difficult asthma clinic more frequently than anticipated, which may have been burdensome for both the patient and investigator and may have negatively affected recruitment. However this had to be countered by the fact that a previous study demonstrating significant improvements on inhaler technique and asthma control over a six month duration required patients to attend their community pharmacy for the intervention to be reinforced at regular intervals (at one, two and three months) (Basheti et al., 2008). Consequently it was considered that this reinforcement

strategy might be critical to improving asthma control and was specified in an early draft of the study protocol.

For practical reasons in this study, community pharmacists were asked to provide this reinforcement role for patients allocated to the intervention group, by using MURs to reinforce inhaler technique and identify other medication related issues (see **Chapter 4.2.1**). To improve uptake by patients who were likely to have busy working lives, it was decided that the MUR could be flexible and take place within four to eight weeks after the initial consultation in the difficult asthma clinic. However, since patients are only allowed one MUR every 12 months (Department of Health, 2013), this prevented patients having more than one reinforcement episode during the study and meant that patients were ineligible for the study if they had already had an MUR that year.

4.8.1 Measures of asthma control and quality of life

Patient questionnaires should be designed to be acceptable for patients to complete; specifically they should be short, reliable, validated and responsive to change (Bowling, 2002). Therefore it was decided that any questionnaire used in this study should comply with these criteria.

As a measure of asthma control, two questionnaires were considered: the ACT (Nathan et al., 2004) and ACQ (Juniper et al., 1999b), which are both recommended by GINA (Global Initiative for Asthma, 2014), the BTS/SIGN (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014), and the ATS/ERS (Reddel et al., 2009). A decision has been made to use the ACQ in this study, as it has been extensively validated in adults aged 17 years or older (Juniper et al., 1999b, Juniper et al., 2005, Juniper et al., 2006) and is widely recognised and used in research and clinical practice, and so was thought to best comply with the requirements for a valid test. Additionally, copyright restrictions prohibited the use of the ACT for financial reasons.

The ACQ has six questions requiring patients to rate their asthma symptoms, use of SABA over the previous week, and one question requiring measurement of their lung function. It is scored on a seven-point scale from 0 (totally controlled) to 6 (severely uncontrolled), with a cut-off for controlled asthma

defined as an ACQ less than 1.0 (Juniper et al., 2006), and a clinically significant improvement in asthma defined as a reduction in ACQ score greater than 0.5 units.

Similarly, to determine quality of life, AQLQ was used since it has been validated in patients aged 16-70 years, and has excellent test-retest reliability, is very responsive to within-patient change over time and can discriminate between patients with different levels of impairment (Juniper et al., 1992, Juniper et al., 1993). However this questionnaire has 32 questions comprising four domains (symptoms, activity limitation, emotional function and environmental stimuli), and so may be less acceptable to patients because of its length. Each question is answered on a 7-point scale (where 7 = not impaired at all, to 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses, and a change in score of 0.5 on the 7-point scale is clinically significant.

Additionally, since quality of life may be compared across different conditions, it is often useful to also use a generic measure that can be used to compare the impact of interventions on quality of life. The European Quality of Life-5 Dimensions Questionnaire (EQ-5D™) (The EuroQol Group, 1990, Brooks, 1996) is a standardised, validated tool for measuring health outcomes that is not specific for any medical condition, but has been used in asthma studies and is recognised as a validated tool in the NICE Guide to the methods of technology appraisals (National Institute for Health and Clinical Excellence, 2008), and so was considered appropriate for use in this study. This questionnaire also includes a patient-reported self-rated health measure using the EQ visual analogue scale (EQ VAS), which allows patients to rate their health on a 20cm vertical visual analogue scale from 0 (‘the worst health you can imagine’) to 100 (‘the best health you can imagine’).

4.8.2 Exhaled nitric oxide

Exhaled Nitric Oxide (FE_{NO}) is a marker of eosinophilic inflammation associated with asthma (Berry et al., 2005, British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014, Michils et al., 2008, Shaw et al., 2007). It is a simple and reproducible test

(Kharitonov et al., 2003) that is commonly used in difficult asthma clinics (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014) and may be measured as a marker of asthma control (Michils et al., 2008). A raised FE_{NO} above 50 ppb has been demonstrated to be predictive of a positive response to inhaled corticosteroids (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Smith et al., 2005a). Since FE_{NO} is reduced with inhaled corticosteroid treatment, it has been postulated that it may be used to guide reductions in maintenance ICS treatment without resulting in loss of asthma control (Smith et al., 2005b), however data on this are currently lacking (Global Initiative for Asthma, 2014). FE_{NO} will be measured in this study to determine whether this may have a value as a marker of the success of the intervention.

4.8.3 Inhaler technique

As outlined in the literature review (**Chapter 3.3.3**), studies investigating interventions to improve inhaler technique vary in study design. Furthermore, these studies and cross-sectional studies of inhaler technique in patients (see **Chapter 2.2.2**) and healthcare professionals (see **Chapter 2.2.4**) vary in the assessment methods and reporting of inhaler technique (Basheti et al., 2014). This is primarily due to the fact that there is no one approved and validated assessment checklist for each inhaler device (Basheti et al., 2014). This study therefore used bespoke inhaler checklists for each inhaler device based upon the manufacturer's instructions and checklists used in previous studies (see **Appendix 8**).

These checklists can be used to determine the proportion of patients with optimal inhaler technique (performing all the correct steps on the checklist), the proportion of patients with satisfactory technique (performing all the critical steps on the checklist, but with some minor errors), and the average inhaler technique score. Each of these outcomes have recently been recommended in one review article that has made recommendations on performing and reporting inhaler technique studies (Basheti et al., 2014).

4.8.4 Inhaler preference

An important factor that may be frequently overlooked when prescribing inhaler devices is to determine each patient's preference of inhaler device as this may affect their adherence to treatment (Capstick and Clifton, 2012, Dolovich et al., 2005), and this was investigated in this study.

All patients in the PI group were trained in the use of Accuhaler, Easi-Breathe, Easyhaler, HandiHaler, pMDI, Respimat and Turbohaler devices, and asked to rank each device in order of preference. Two scoring systems were used to evaluate overall patient preference, the first using a previously published method used in one independent patient preference study (Lenney et al., 2000). This study allocated each patient's first choice device a score of 3 points, second choice was 2 points and third choice was 1 point, then the points added to give an overall score for each device.

Since this scoring system does not allocate scores to devices consistently ranked outside the top 3, it may not adequately establish the rank of these lesser-preferred devices. The alternative preference scoring system used in the present study allocated 7 points to each patient's first choice device, 6 points for their second choice, 5 points for their third, 4 points for their fourth, 3 points for their fifth, 2 points for their sixth and 1 point for their seventh choice. The total score was added to give an overall score for each device, and the devices ranked in order of highest total score.

4.8.5 Adherence

In order to measure adherence, a number of strategies were considered including GP records and community pharmacy patient medication records. This is a simple method to assess adherence (Murphy et al., 2012b), but may not be accurate if patients are not actually taking/using their medication. Consequently, an additional tool was considered necessary to measure adherence, and the MARS (Horne and Weinman, 2002) was used. This is a self-report questionnaire that utilises non-threatening questions in order to encourage patients to openly describe their medication adherence, and has been validated in a study comparing asthma patient's self-reporting to pharmacy prescribing records (Menckeberg et al., 2008). It has been well

validated in asthma patients, and therefore increases confidence in the accuracy of the adherence results produced. However patients were asked to answer the questions in the context of their use of ICS rather than all their asthma medicines as a whole, so that comparisons could be made between patients in terms of adherence to regular preventer therapy. There was a risk with the use of an additional questionnaire as it could potentially over burden patients with questionnaires. Furthermore, there is a risk of acquiescence responses (Bowling, 2002) with the MARS questionnaire if patients felt compelled to report good adherence for fear of disappointing the investigator. This could potentially have been combatted by asking patients to seal this questionnaire in an envelope, but this was discounted as a solution as it may have been useful for the asthma consultation.

A final tool used in the study was the Beliefs about Medicines Questionnaire (BMQ), which has been validated for use in patients with asthma (Horne et al., 1999), and has been recommended as a useful intervention to facilitate optimal adherence (Haughney et al., 2008). The BMQ was thought to be useful for identifying potential perceptual and practical barriers to adherence in individual patients, because it assesses each patient's beliefs about the need for regular preventer therapy for controlling their asthma, and also assesses their concerns about potential adverse effects of treatment.

4.8.6 Exacerbations of asthma

The constraints of time and resource within the initial clinic appointments prevented the use of use of asthma diaries to document asthma symptoms, lung function, symptom-free days, side effects, and use of reliever inhaler on a daily basis. This also prevented patients prospectively documenting any exacerbations requiring OCS use, hospital admissions or attendance at the A&E department. Consequently retrospective measures were used to collect these data, including GP records, the hospital patient database 'Patient Centre' (which collects data on admissions and outpatient clinic appointments) and hospital pharmacy patient medication records.

Whilst diaries are thought to be more accurate to collect information on asthma exacerbations, because data can be recorded by patients on a prospective

basis, this relies on recruiting patients who would be motivated to do this (Reddel et al., 2009). Additionally, it was thought to be an extra burden to instruct patients on how to complete the diaries, and what they would need to record, and so the use of diaries was discounted. Instead indirect measures recommended by the ATS and ERS were decided upon (Reddel et al., 2009).

The downside to this is that since asthma is, by the very nature of the condition, associated with significant variation in symptoms over time, a lot of data may be lost by not using a patient diary. Consequently data collected at baseline and at six months maybe subject to chance variation in patient's condition and chance exposure to exacerbating factors in the period running up to each appointment, which could interfere with outcomes that measure the impact of the intervention. However this would be the same for patients in both the intervention and control groups, and so this effect may be balanced across the groups.

4.9 Analysis plan

It was anticipated that the primary outcome of ACQ would produce ordinal data that would not be normally distributed, but it was planned to confirm this by looking at histograms of the data, measuring p-p plots, and by using the Kolmogorov-Smirnov test.

For the primary outcome measure, planned statistical tests included change in ACQ from baseline within groups using the Wilcoxon test for non-parametric data, whilst the difference in ACQ between the two intervention groups was planned to be tested using the Mann-Whitney test for non-parametric data.

Similarly, it was planned to test for normality of data for the secondary outcomes by looking at histograms of the data, measuring p-p plots, and by using the Kolmogorov-Smirnov test. Planned statistical tests are outlined in **Table 4**.

Table 4. Planned statistical tests on secondary outcome measures.

Measure	Type of Data	Data Description	Statistical Test (between groups)	Statistical Test (within group)
Standardised Asthma Quality of Life Questionnaire (AQLQ(S))	Ordinal	Non-parametric	Mann-Whitney	Wilcoxon
European Quality of Life-5 Dimensions (EQ-5D-5L)	Ordinal	Non-parametric		
Number of steroid courses within the previous 6 months	Scale (ratio)	Non-parametric (expected)	Mann-Whitney	Wilcoxon
Number of A&E attendances and hospitalisations within the previous 6 months	Scale (ratio)	Non-parametric (expected)	Mann-Whitney	Wilcoxon
Lung function (FEV1, FEV1/FVC)	Scale (ratio)	parametric	Paired samples T test	Independent samples T test
Exhaled Nitric Oxide	Scale (ratio)	Non-parametric (expected)	Mann-Whitney	Wilcoxon
Inhaler technique score	Ordinal	Non-parametric (expected)	Mann-Whitney	Wilcoxon
Ability to use prescribed inhaler device before and after instruction	Nominal		Chi-square	Wilcoxon
Inspiratory flow before and after instruction through prescribed inhaler device	Scale (ratio)	Non-parametric (expected)	Mann-Whitney	Wilcoxon
Adherence (Patient reported [MARS and BMQ], GP reported [based on prescription data].	Ordinal	Non-parametric (expected)	Mann-Whitney	Wilcoxon
Interventions	Nominal		Chi-square	n/a
MUR data: 1. Interventions 2. GP referrals 3. Adherence 4. Inhaler technique	Nominal (all)		Chi-square	Wilcoxon

4.9.1 Exploratory analysis plan

Since this study is classed as a complex interventional study, the effects of different components of the intervention on asthma control and other outcomes will be explored.

4.9.1.1 Effect of Pharmacist education

It is anticipated that the intervention will improve all outcomes:

1. Improvement on adherence (Patient reported [MARS and BMQ], GP reported [based on prescription data], Community Pharmacist reported [based on prescriptions dispensed])
2. Asthma control, measured using ACQ

3. Quality of life, measured using AQLQ(S) and EQ-5D-5L
4. Number of exacerbations, defined as OCS courses and hospital or A&E visits
5. Exhaled nitric oxide
6. Lung function, measured using FEV_1 and FEV_1/FVC ratio
7. Inhaler technique at 6 months

4.9.1.2 Inhaler technique at 6-months

Patients recruited to the pharmacist intervention group will have received intensive education and training on the correct use of inhaler devices. If good technique is maintained from baseline to 6-months, it is anticipated that this will have a positive impact on the following outcome measures:

1. Asthma control, measured using ACQ
2. Quality of life, measured using AQLQ(S) and EQ-5D-5L
3. Number of exacerbations, defined as OCS courses and hospital or A&E visits
4. Exhaled nitric oxide
5. Lung function, measured using FEV_1 and FEV_1/FVC ratio

4.9.1.3 Effect of adherence rates

It is anticipated that patients with high levels of adherence to their preventer therapy (ICS or combined ICS/LABA) will be associated with improvements in all outcomes:

1. Asthma control, measured using ACQ
2. Quality of life, measured using AQLQ(S) and EQ-5D-5L
3. Number of exacerbations, defined as OCS courses and hospital or A&E visits
4. Exhaled nitric oxide
5. Lung function, measured using FEV_1 and FEV_1/FVC ratio

4.9.1.4 Effect of MUR

It was anticipated that not all of the patients randomised to the intervention group would have their planned MUR. Therefore, a subgroup analysis study will be performed to determine differences in all outcome measures between the following subgroups:

1. Pharmacist Intervention with MUR
2. Pharmacist Intervention without MUR

4.10 Ethical considerations

This study was reviewed and given favourable opinion by Humber Bridge Research Ethics Committee on 5th July 2012 (**Appendix 11**), and was approved by Research & Development at Leeds Teaching Hospitals on 27th July 2012 (**Appendix 12**).

A number of ethical issues were identified in the study, mainly due to the perceived risks associated with changing current clinical practice, in particular associated with patients having an asthma review from a pharmacist rather than a doctor, and also asking patients to refrain from having a MUR for the duration of the study.

On the first issue, this study recruited patients to receive an asthma review from an advanced clinical pharmacist rather than their usual care, which could comprise an asthma review from a consultant physician, specialist registrar or asthma nurse specialist. It was considered that there was a potential risk that the pharmacist review may not be as comprehensive or on a comparative level to established members of the asthma team. Consequently, the advanced clinical pharmacist, who already had knowledge, skill and expertise in asthma, spent several weeks observing consultations and had their asthma reviews supervised by the lead clinician for the difficult asthma service in order to ensure consistent and appropriate management. Additionally the study design allowed for the advanced clinical pharmacist to seek advice on complex issues during the consultation despite independent practice, which is consistent with the operation of healthcare professionals in outpatient settings where advice and opinions may be sought on individual complex cases.

On the second issue, asking patients in the usual care to not have a MUR was considered to be potentially ethically problematic by denying some patients a commissioned healthcare service. However an audit of patients attending the difficult asthma clinic found that only half of the patients who were eligible for a

MUR had been offered one (Capstick et al., 2012), and only a third of patients had received an MUR. This suggests that the uptake for the MUR service is sub-optimal in this patient group, and that asking patients to avoid having an MUR would affect relatively few of them.

4.11 Study sponsorship

This report is independent research commissioned by the Pharmaceutical Trust for Educational and Charitable Objects (now known as Pharmacy Research UK). The views expressed in this publication are those of the author and not necessarily those of the Pharmaceutical Trust for Educational and Charitable Objects.

4.12 Dissemination of findings

It is anticipated that the results will be published in a peer-reviewed scientific journal (e.g. pharmacy practice or respiratory specialist medical journals), and presented at local, national or international meetings. Potential areas for publication include: (i) the impact of pharmacist interventions on asthma control and quality of life; (ii) the impact of pharmacist training on inhaler technique at baseline and at 6 months; (iii) adherence in patients with difficult asthma.

The results of this research project will be disseminated internally within the Leeds Teaching Hospitals NHS Trust by presenting to the pharmacy and respiratory medicine departments, and by writing a business case to demonstrate the need for on going pharmacist involvement within the Leeds difficult asthma clinic.

It is anticipated that the results will be shared with community pharmacists in the form of the executive summary report via Community Pharmacy West Yorkshire.

5 Results

5.1 Introduction

Outcome measures used in the study were based on the ATS/ERS statement on standardising endpoints for clinical asthma trials and clinical practice (Reddel et al., 2009).

The data generated in the study were analysed to determine whether there were any significant differences between the PI group and UC group at baseline, or at follow-up, and also to determine whether any significant effects had occurred as a result of the interventions performed. To help ensure the validity of statistical testing, all data collected were characterised as scale, ordinal or nominal. Scale data were further assessed for normality. Normality was tested for all data collected using histograms, P-P plots and Kolmogorov-Smirnov tests using SPSS Statistics version 21.0.0.0 (© Copyright IBM Corporation). These data are presented in **Appendix 13**.

5.2 Baseline demographics

Of the 188 patients screened for inclusion in the study, a total of 52 patients were recruited to the study between 25th September 2012 and 29th October 2013. Twenty-six were randomly assigned to the PI group and 26 to the UC group. Forty-seven patients (24 in the PI group) were followed up for a median (interquartiles, IQ) of 182 (175, 203) days and were included in the intention to treat analysis. Only six participants (23%) in the PI group received a t-MUR at a mean of 60 days (range 28 – 143 days) following randomisation (see **Figure 5**). All but one of the participants received their t-MUR within the four to eight week range stipulated in the protocol. The mean (SD) age of participants was 46.9 (12.4) years, and there were slightly more female (63.5%) than male participants. Almost half of all participants had never smoked (48.1%) and only 11.5% were current smokers. There were no significant differences in the demographic characteristics between participants in the PI and UC group at baseline (see **Table 5**).

The median (IQ) duration of asthma instability was 3.50 (1.17, 8.75) years and the majority of patients were currently prescribed asthma medicines at Step 4 or

5 of the BTS/SIGN asthma guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014), with all patients prescribed a high dose ICS at a median (IQ) equivalent beclometasone-CFC dose of 1600 (800, 2000) micrograms. Most patients were prescribed a LABA in a combination ICS/LABA inhaler, except one who was prescribed separate ICS and LABA inhalers to allow ciclesonide to be prescribed (due to the oropharyngeal adverse effects of alternative ICS). The most common additional controller medicines prescribed were LKTa (65.4%), methylxanthines (30.8%), and long-acting muscarinic antagonists (LAMA) (17.3%). Most patients in the UC group were prescribed a SABA reliever inhaler, except one who was prescribed the Symbicort® maintenance and reliever therapy regimen. Participants reported a mean (SD) of 4.8 (3.22) emergency courses of OCS in the past 12 months and a median of 1 hospital admission or A&E department visit within the past 12 months, which is typical of patients with difficult asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014).

Participants recruited to the study had uncontrolled asthma at baseline, with a median (IQ) ACQ score of 3.00 (2.14, 3.57) across both groups, a median (IQ) exhaled nitric oxide (FeNO) of 36.0 (15.0, 67.0) ppb, and were using were using a median (IQ) 49.0 (21.0, 75.75) puffs of SABA inhaler each week. As is characteristic of asthma, a wide variation in lung function was observed on spirometry testing, with a mean (SD) FEV_1/FVC ratio of 69.34 (10.73) (range 47.95 to 90.83), and a FEV_1 of 71.79 (19.13) % of predicted (range 36.60% to 123.00%). Participants in the PI group had worse asthma control at baseline than those in the UC group based ACQ score, SABA use, emergency courses of OCS in the past 12 months and duration of asthma instability, although this did not reach statistical significance (see **Table 5**).

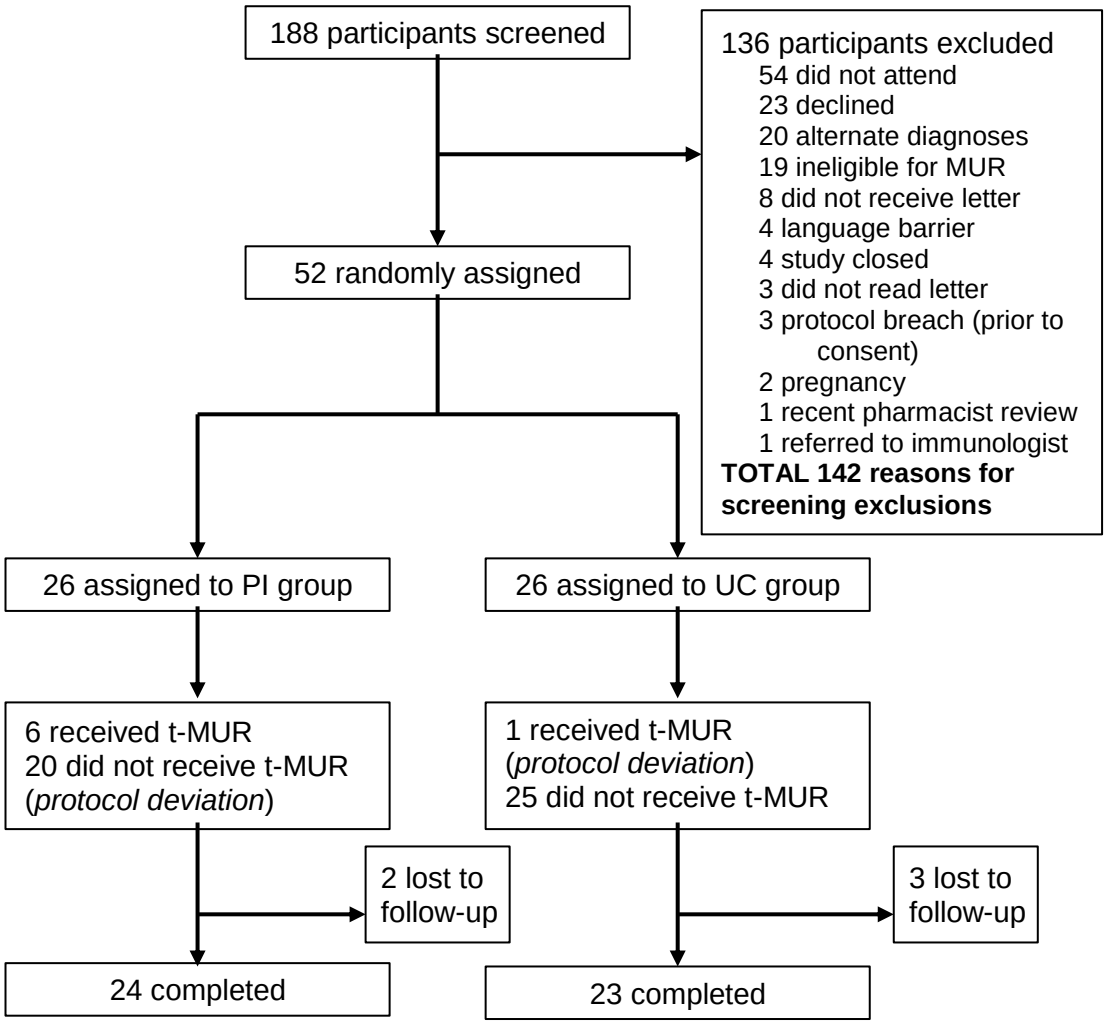


Figure 5. CONsolidated Standards of Reporting Trials (CONSORT)/patient flow diagram.

PI, pharmacist intervention group; UC, usual care group; t-MUR, targeted medicines use review.

Table 5. Baseline demographic data

	PI group	UC group	Statistical Test	Value	p value
Number of participants	26	26			
Sex (Female; n, %)	17 (65.4%)	16 (61.5%)	Fisher's Exact Test	0.083	1.000
Exact age at recruitment (mean years (SD))	46.36 (12.88)	47.71 (12.14)	Independent samples t-test	-0.330	0.743
Baseline Smoking Status: Never Smoked (n, %) Ex-smoker (n, %) Current Smoker (n, %)	 13 (50.0%) 10 (38.5%) 3 (11.5%)	 12 (46.2%) 11 (42.3%) 3 (11.5%)	Chi-Square	0.0088	0.957
Duration of asthma instability (median years, IQ)	5.0 (2.0, 10.0)	2.5 (1.0, 6.5)	Mann-Whitney	261.500	0.161
Steroid courses in previous 12 months (mean (SD))	5.62 (3.62)	3.92 (2.50)	Independent samples t-test	1.942	0.059
Steroid courses in previous 3 months (median, IQ)	2.0 (1.0, 3.0)	1.0 (0.0, 2.0)	Mann-Whitney	266.500	0.179
Hospital admissions and A&E visits in previous 12 months (median, IQ)	1.0 (0.0, 1.25)	1.0 (0.0, 1.25)	Mann-Whitney	325.500	0.808
Hospital admissions and A&E visits in previous 3 Months (median, IQ)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	Mann-Whitney	327.000	0.819
Number of puffs of reliever (SABA) inhaler per week (median, IQ)	49.0 (33.25, 64.75)	45.5 (12.5, 90.5)	Mann-Whitney	328.000	0.854
ACQ (median, IQ)	2.86 (2.25, 3.25)	3.00 (1.96, 3.71)	Mann-Whitney	333.000	0.927
AQLQ(S) (median, IQ)	4.11 (3.38, 5.21)	3.77 (2.87, 5.30)	Mann-Whitney	310.500	0.615
FEV_1 (% predicted; mean (SD))	72.92 (20.06)	70.57 (18.41)	Independent samples t-test	0.432	0.668
FEV_1/FVC (mean (SD))	69.46 (11.05)	69.21 (10.61)	Independent samples t-test	0.079	0.937
FeNO (median, IQ)	38.0 (19.0, 70.75)	27.0 (14.0, 67.0)	Mann-Whitney	110.000	0.693
Possession of Asthma Action Plan (n, %)	16 (61.5%)	15 (57.7%)	Fisher's Exact Test	0.080	1.000

	PI group	UC group	Statistical Test	Value	p value
Current asthma treatment:					
ICS (n, %)	1 (3.8%)	2 (7.7%)		0.354	1.000
ICS/LABA (n, %)	25 (96.2%)	26 (100%)		1.020	1.000
LABA (n, %)	1 (3.8%)	0 (0%)		1.020	1.000
LKTa (n, %)	18 (69.2%)	16 (61.5%)		0.340	0.771
Methylxanthine (n, %)	7 (26.9%)	9 (34.6%)	Fisher's Exact Test	0.361	0.764
SABA (n, %)	26 (100%)	25 (96.2%)		1.020	1.000
LAMA (n, %)	4 (15.4%)	5 (19.2%)		0.134	1.000
Anti-IgE (n, %)	0 (0%)	0 (0%)		n/a	n/a
Prednisolone (n, %)	5 (19.2%)	3 (11.5%)		0.591	0.703
Methotrexate (n, %)	0 (0%)	2 (7.7%)		2.080	0.490
Baseline equivalent beclometasone-CFC dose (micrograms; median, IQ)	1600 (800, 2000)	2000 (800, 2000)	Mann-Whitney	293.000	0.394

PI, pharmacist intervention group; UC, usual care group; SD, standard deviation; IQ, interquartiles; ACQ, Juniper's asthma control questionnaire; AQLQ(S), Juniper's standardised asthma quality of life questionnaire; FEV_1, forced expiratory volume in one second; FEV_1/FVC, ratio of forced expiratory volume in one second / forced vital capacity; FeNO, exhaled nitric oxide; ICS, inhaled corticosteroid; ICS/LABA, inhaled corticosteroid / long-acting $beta_2$-agonist combination inhaler; LABA, long-acting beta2-agonist; LKTa, leukotriene receptor antagonist; SABA, short-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; anti-IgE, humanised monoclonal antibody that selectively binds to immunoglobulin E.

5.3 Interventions

This study was designed as a pragmatic (real-life) complex intervention study. The intervention comprised a number of possible issues that could be identified and addressed during a routine consultation in the difficult asthma clinic. Since this was a real-life study, appointments were prolonged due to the assessments performed in addition to the verbal consultation, which meant that many patients spent between one and two hours in the clinic, although it was not practical to perform accurate time keeping.

5.3.1 Number of interventions

At the initial consultation, participants randomised to the PI group received significantly more interventions than those in the UC group (79 vs. 34 respectively; Mann-Whitney U=96.5, p<0.001) (see **Table 6**). Each patient received a median (IQ) of 3 (2, 4) interventions in the PI group, compared to 1 (0, 2) in the UC group. In contrast, those in the UC group were significantly more likely to receive no interventions during their consultation (7 vs. 0 patients; χ^2 8.089, p=0.010; Fisher's Exact Test).

Participants in the PI group received more interventions within each specified category compared to those in the UC group (**Table 6**), including: medication-related issues (54 vs. 18); allergy tests and asthma investigations (5 vs. 1); management of associated medical conditions (6 vs. 4); and education or advice (14 vs. 11). Despite the lower number of interventions performed overall, inhaler technique training was the only specific intervention that significantly more participants received in the PI group (24 vs. 4; χ^2 30.952, p<0.001; Fisher's Exact Test).

Provision of asthma action plans as part of the intervention in both groups increased the proportion of patients possessing these: from 61.5% to 83.3% of participants in the PI group; and from 57.7 to 73.9% in the UC group. Possession rates were not statistically different between the two groups.

5.3.2 Inhaler technique at baseline

5.3.2.1 Devices prescribed

A total of 96 inhaler devices were prescribed for the 52 participants recruited to the study, with the majority using two different inhaler devices (n=34). Only 11 patients were prescribed just one type of inhaler device, whilst five had three different devices. The most frequently prescribed devices were pMDI (67.3%), Turbohaler (61.5%) and Accuhaler (26.9%) for all patients in both groups. The types of inhaler devices prescribed were similar for participants in the PI and UC group, with no significant difference in the proportion of participants prescribed each device (**Table 7**).

5.3.2.2 Previous training

Almost all participants in the study had previously received inhaler technique training, most commonly from hospital nursing staff (usually in the difficult asthma clinic) or practice nurses in GP surgeries. Training from physicians and pharmacists in primary and secondary care was reported less commonly (**Table 8**).

Table 6. Interventions made during asthma consultation

Classification of intervention	Intervention	PI (n=26)		UC (n=26)		All (n=52)		Chi Square (Fisher's Exact Test)	p value
		n	%	n	%	n	%		
Management of Associated Medical Condition	Investigation for additional diagnosis (e.g. cor pulmonale, VCD, bronchiectasis), or psychological referral	0	0.0%	0	0.0%	0	0.0%	n/a	
	Reflux	4	15.4%	2	7.7%	6	11.5%	0.754	0.668
	Rhinitis	2	7.7%	2	7.7%	4	7.7%	0.000	1.000
Education / Advice	Allergen avoidance	1	3.8%	0	0.0%	1	1.9%	1.020	1.000
	Asthma Action Plan provision / monitoring	3	11.5%	6	23.1%	9	17.3%	1.209	0.465
	Healthy Living (exercise, smoking cessation, weight management)	4	15.4%	1	3.8%	5	9.6%	1.991	0.350
	Medication / Adherence	6	23.1%	4	15.4%	10	19.2%	0.495	0.726
Medication	Optimise dose of asthma medicines / maintenance OCS	4	15.4%	4	15.4%	8	15.4%	0.000	1.000
	Addition of new asthma medication	4	15.4%	3	11.5%	7	13.5%	0.165	1.000
	Inhaler Device Switch	9	34.6%	3	11.5%	12	23.1%	3.900	0.097
	Inhaler Technique +/- provision of training aid / spacer	24	92.3%	4	15.4%	28	53.8%	30.952	<0.001
	Consideration for omalizumab	1	3.8%	1	3.8%	2	3.8%	0.000	1.000
	Stop non-essential / non-effective asthma medicine	3	11.5%	2	7.7%	5	9.6%	0.221	1.000
	ADR advice / management	2	7.7%	0	0.0%	2	3.8%	2.080	0.490
	Acute course OCS	3	11.5%	1	3.8%	4	7.7%	1.083	0.610
	Theophylline TDM	4	15.4%	0	0.0%	4	7.7%	4.333	0.110
Tests	Allergy testing / investigations	5	19.2%	1	3.8%	6	11.5%	3.014	0.191
None	No intervention required	0	0.0%	7	26.9%	7	13.5%	8.089	0.010

PI, pharmacist intervention group; UC, usual care group; N, number of patients in intervention group; n, number of participants receiving specific intervention; VCD, vocal cord dysfunction; OCS, oral corticosteroid; TDM, therapeutic drug monitoring.

Table 7. Inhaler devices prescribed at baseline

	PI (n=26)		UC (n=26)	
	n	**%**	**n**	**%**
Accuhaler	10	38.5%	4	15.4%
Easi-Breathe	2	7.7%	2	7.7%
Easyhaler	0	0%	0	0%
HandiHaler	4	15.4%	2	7.7%
pMDI	17	65.4%	18	69.2%
pMDI + Spacer	2	7.7%	1	3.8%
Respimat	0	0%	2	7.7%
Turbohaler	17	65.4%	15	57.7%
Total Number of Inhaler Devices prescribed	**52**		**44**	

PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler. The proportion of participants in the PI and UC groups prescribed each device was not statistically significant (Fisher's Exact Test).

Table 8. Previous inhaler technique training.

	PI (n=26)	UC (n=26)
Hospital Respiratory Nurse	18	18
Practice Nurse	9	8
Hospital Respiratory Physician	2	2
Hospital non-Respiratory Physician	0	1
GP	2	5
Hospital Pharmacist	3	2
Community Pharmacist	1	4
Never Checked	1	3

PI, pharmacist intervention group; UC, usual care group.

5.3.2.3 Inspiratory flow

Analysis of patients' peak inspiratory flow rate (IFR) through different devices demonstrated that some data were normally distributed, whilst others were not normally distributed. As a consequence, non-parametric statistical tests were used for data analysis, specifically Mann-Whitney for two independent samples, and Wilcoxon for two related samples (Campbell and Machin, 1999).

At baseline, participants in the PI group were assessed to have a significantly faster median (IQ) peak IFR than participants in the UC group through pMDI devices 130.0 (93.8; 153.8) L/min vs. 55.0 (43.0; 120.0) L/min; Mann-Whitney U 32.0, $p<0.001$ and Accuhaler devices 75.0 (68.8; 121.3) L/min vs. 55.0 (31.3; 67.5) L/min; Mann-Whitney U 6.5, $p=0.021$, but not through Turbohaler devices 65.0 (62.5; 75.0) L/min vs. 78.0 (70.0; 85.0) L/min; Mann-Whitney U 62.5, $p=0.013$.

Education on the correct IFR achieved a significant reduction in the median (IQ) peak IFR through pMDI devices to 57.5 (48.8; 60.0) L/min (Wilcoxon Z -3.623, p<0.001) in the PI group, but achieved no significant change in median peak IFR through other devices in the PI group, and no significant effect for any device in the UC group (see **Figure 6**).

Consequently, more patients achieved the correct IFR after education in the PI group (**Figure 7**) through: pMDI (one before education compared to 15 after education); Accuhaler (9 before education compared to 14 after education); and Easi-Breathe devices (0 before education compared to 2 after education). There was limited effect observed in the UC group, with no increases in the number of patients achieving the correct IFR for any device. This was in part due to fewer IFR assessments being performed (4, 0 and 2 assessments for Accuhaler, HandiHaler and Easi-Breathe inhalers respectively).

5.3.2.4 The effect of education on inhaler technique score

Interim baseline data on the inhaler technique of the first 25 patients recruited to the study was presented at the 2013 European Respiratory Society Congress (Capstick et al., 2013). This highlighted that at least one critical error was made in 57% of inhaler technique assessments, whilst optimal technique was found in only 31% of assessments.

When inhaler technique was assessed for all the recruited patients, using inhaler technique score calculated as a percentage of all the steps performed correctly, technique scored relatively highly (>80%) for the most commonly prescribed devices: pMDI, Accuhaler and Turbohaler. It was not significantly different between patients in the PI and UC group. Across both groups, the mean, SD inhaler technique score was highest for Turbohaler (93.75, 6.60), followed by Accuhaler (91.36, 15.03), then pMDI, (80.26, 17.70). In addition, inhaler technique scores were higher than pMDI alone for: Easi-Breathe, Easyhaler, HandiHaler and pMDI with spacer. This may be an artefact due to the small numbers of patients prescribed these devices (ranging from one to five patients).

Since inhaler technique was not perfect for any of the devices, further training was provided. The improvements in mean, SD inhaler technique score for the three most commonly used inhaler devices are presented in **Figure 8**. Significant improvements were observed for participants in the PI group using pMDI (from 80.30, 7.38 to 97.33, 4.27; Wilcoxon -3.677, p<0.001), Accuhaler (from 94.87, 7.34 to 98.41, 5.94; Wilcoxon -2.121, p=0.034) and Turbohaler devices (from 91.76, 6.36 to 99.41, 2.43; Wilcoxon -3.357, p=0.001). In contrast, significant improvements were only observed in participants in the UC group using pMDI devices (from 80.21, 24.32 to 95.72, 10.22; Wilcoxon -2.527, p<0.001).

The most common errors in inhaler technique included failure to prime the inhaler device correctly (e.g. priming Turbohaler in the vertical position, priming Accuhaler during rather than before inhalation), incorrect inspiratory flow, and poor coordination.

5.3.2.5 Classification of inhaler technique

Inhaler technique was assessed for patients in both the PI and UC groups using the same checklists (**Appendix 8**) and was classified as optimal (no errors made), satisfactory (some minor errors, but no critical errors), or as unsatisfactory (at least one critical error) (Basheti et al., 2005, Basheti et al., 2014). Based on this categorising system, less than half of patients across both study groups had optimal inhaler technique using pMDI and Turbohaler devices at baseline. More patients had optimal inhaler technique using Accuhaler devices than with Turbohaler or pMDI devices (58.8% vs. 46.9% and 17.6%, respectively).

Significantly more patients in the PI group compared to the UC group were assessed to be using their prescribed pMDI and Turbohaler inhalers with an unsatisfactory technique at baseline (pMDI: 17/17 vs. 10/17; Chi-Square 8.815, p=0.012; Turbohaler: 12/17 vs. 3/15; Chi-Square 8.977, p=0.011). There was no significant difference in baseline assessment of inhaler technique for other devices between participants in the PI group and UC group, although low use of alternative devices is likely to have contributed to this.

After education by the pharmacist within the PI group, or clinic nurse in the UC group, the proportion of patients who achieved optimal technique increased for the commonly used inhaler devices pMDI, Accuhaler and Turbohaler (**Figure 9**). A statistically significant increase in the proportion of patients with optimal inhaler technique was observed for pMDI and Turbohaler devices in the PI group, but only for the pMDI device in the UC group. In the PI group, the proportion of patients who had optimal inhaler technique after education increased from 0% to 70.6% for pMDI (Fisher's Exact Test 18.545, $p<0.001$), 58.3% to 92.3% for Accuhaler (Fisher's Exact Test 3.949, $p=0.073$), and from 29.4% to 88.2% for Turbohaler (Fisher's Exact Test 12.143, $p=0.001$). Similarly in the UC group, the proportion of patients who had optimal inhaler technique after education increased from 35.3% to 82.4% for pMDI (Fisher's Exact Test 7.771, $p=0.005$), 60.0% to 100.0% for Accuhaler (Fisher's Exact Test 2.50, $p=0.444$), and from 66.7% to 80.0% for Turbohaler (Fisher's Exact Test 0.682, $p=0.682$).

Despite education, a significant proportion of patients persisted in being assessed as having unsatisfactory inhaler technique, including pMDI (29.4% and 17.6% in the PI and UC groups respectively), Accuhaler (7.7% in the PI group), and Turbohaler (5.9% and 6.7% in the PI and UC groups respectively).

5.3.2.6 Preference

All patients in the PI group were trained in the use of Accuhaler, Easi-Breathe, Easyhaler, HandiHaler, pMDI, Respimat and Turbohaler devices, and asked to rank each device in order of preference, and two scoring systems used to evaluate overall patient preference.

Preference based on the method used in one independent patient preference study (each patient's first choice device scores 3 points, second choice scores 2 points and third choice scores 1 point, then the points added to give an overall score and ranking (Lenney et al., 2000)) demonstrated that the overall preferred inhaler device was the Easi-Breathe, followed by pMDI and Turbohaler (see **Table 9**). Devices that were not frequently used prior to the study such as Respimat, HandiHaler and Easyhaler scored poorly, despite the fact that Easi-Breathe devices were also infrequently used.

The alternative preference scoring system used in this study (each patient's first choice devices scores 7 points, second choice scores 6 points, third choice scores 5 points, fourth choice scores 4 points, fifth choice scores 3 points, sixth choice scores 2 points, seventh choice scores 1 point, then the points added to give an overall score and ranking. This method ranked inhaler devices in similar order of preference to the Lenney method, although Turbohaler scored slightly higher than pMDI (**Table 10**). Of the three least preferred devices, this method may more accurately demonstrate that HandiHaler was the least preferred device compared to Respimat and Easyhaler device in contrast to the Lenney method.

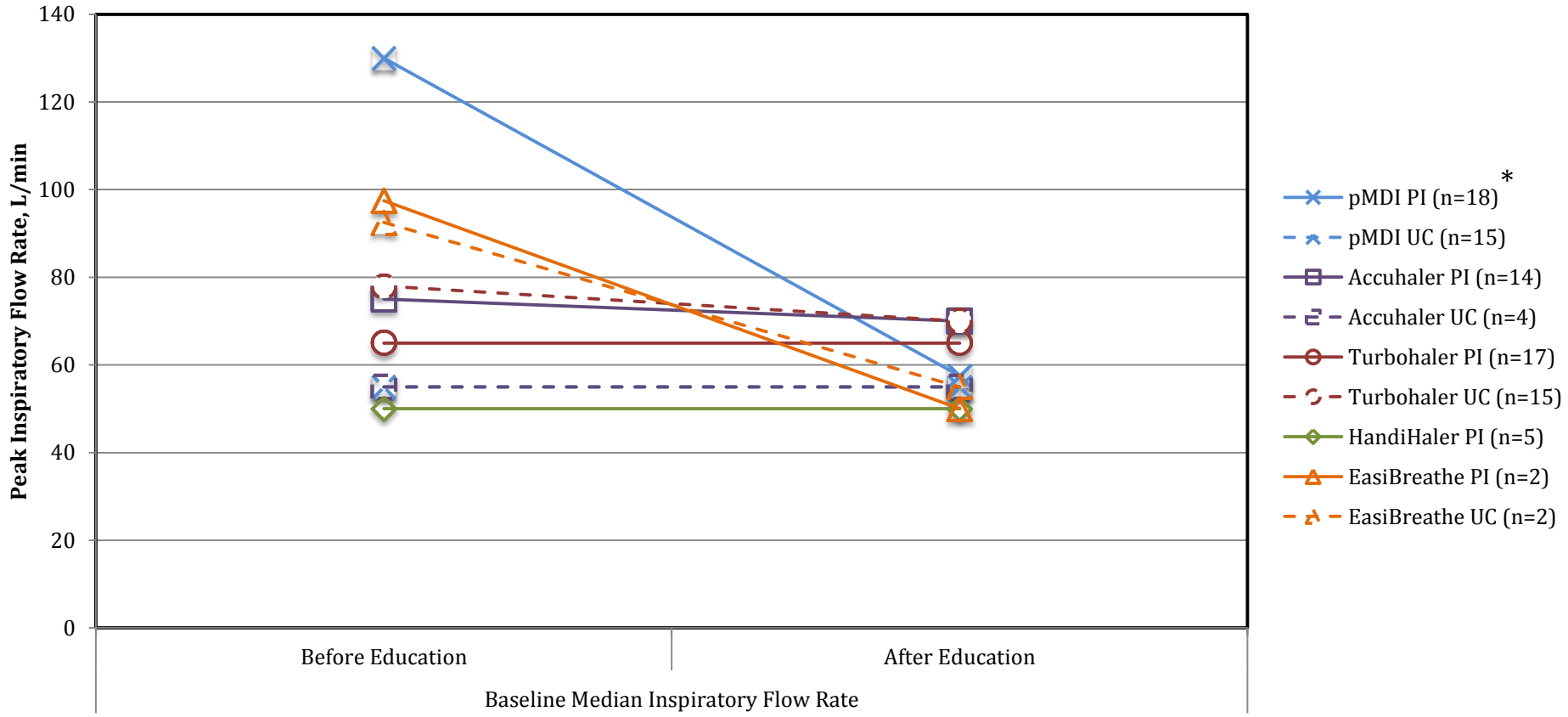


Figure 6. Peak inspiratory flow rate through inhaler devices before and after education at baseline.

PI, pharmacist intervention group (bold lines); UC, usual care group (dashed lines); pMDI, pressurised metered dose inhaler (target inspiratory flow 25-60 L/min); Accuhaler (target inspiratory flow 30-90 L/min); Turbohaler (target inspiratory flow 30-90 L/min); HandiHaler (target inspiratory flow 20-60 L/min); Easi-Breathe (target inspiratory flow 20-60 L/min). *Improvement in peak IFR for pMDI PI $p<0.001$.

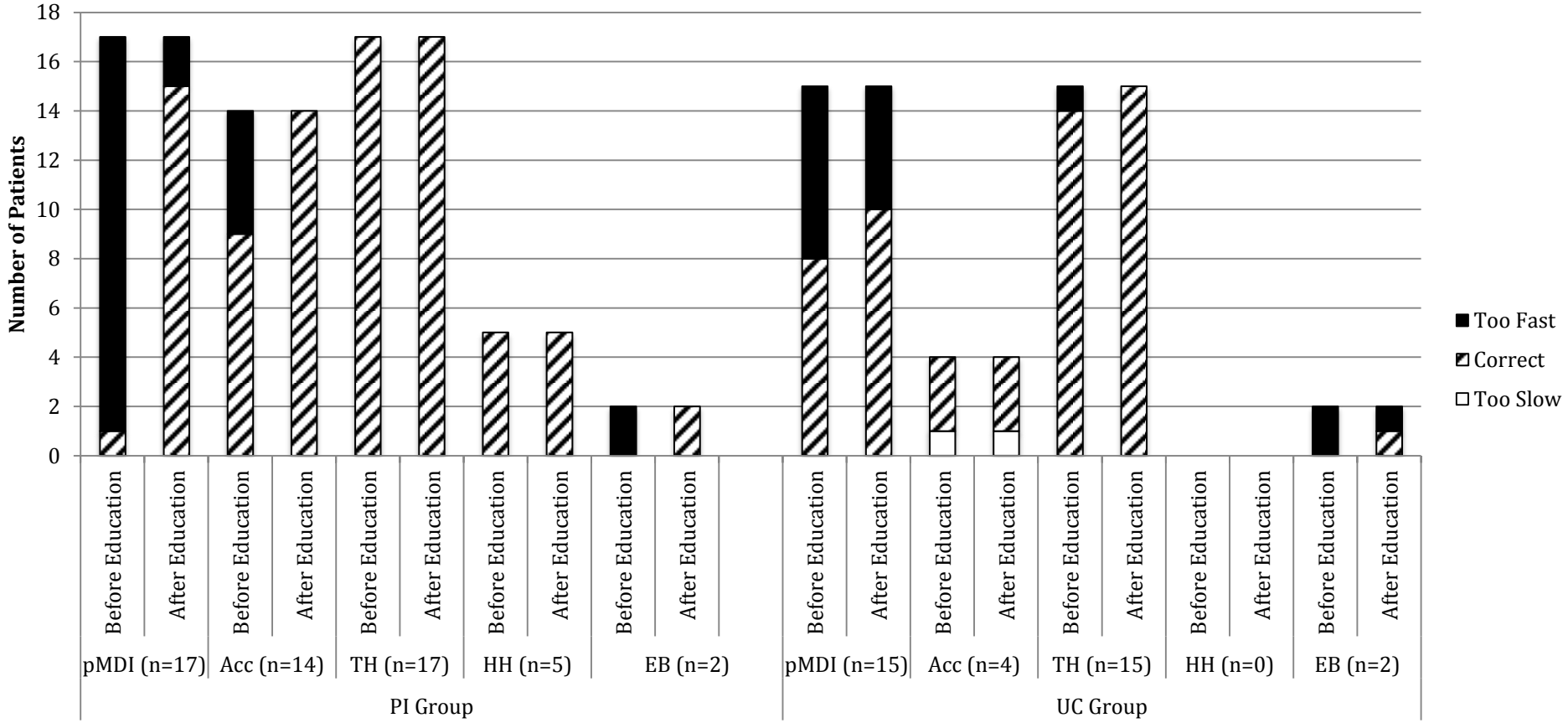


Figure 7. Effect of education on the number of patients with correct peak inspiratory flow rate through inhaler devices at baseline.

PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; HH; HandiHaler; EB, Easi-Breathe.

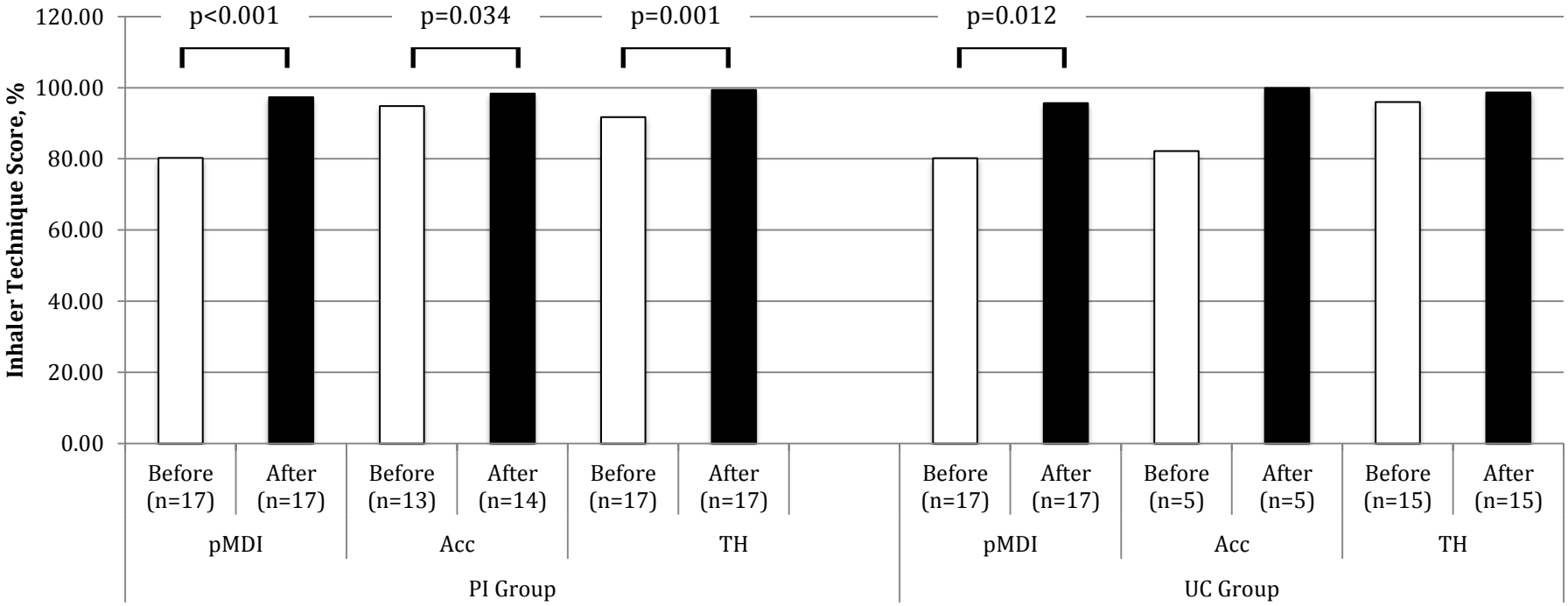


Figure 8. Effect of education on inhaler technique score (% of each step performed correctly) at baseline, before and after education for the three most commonly used inhaler devices.

(Data for all inhaler devices are presented in **Figure 20, Appendix 14**). PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; HH. Improvements in inhaler technique assessed using Wilcoxon test.

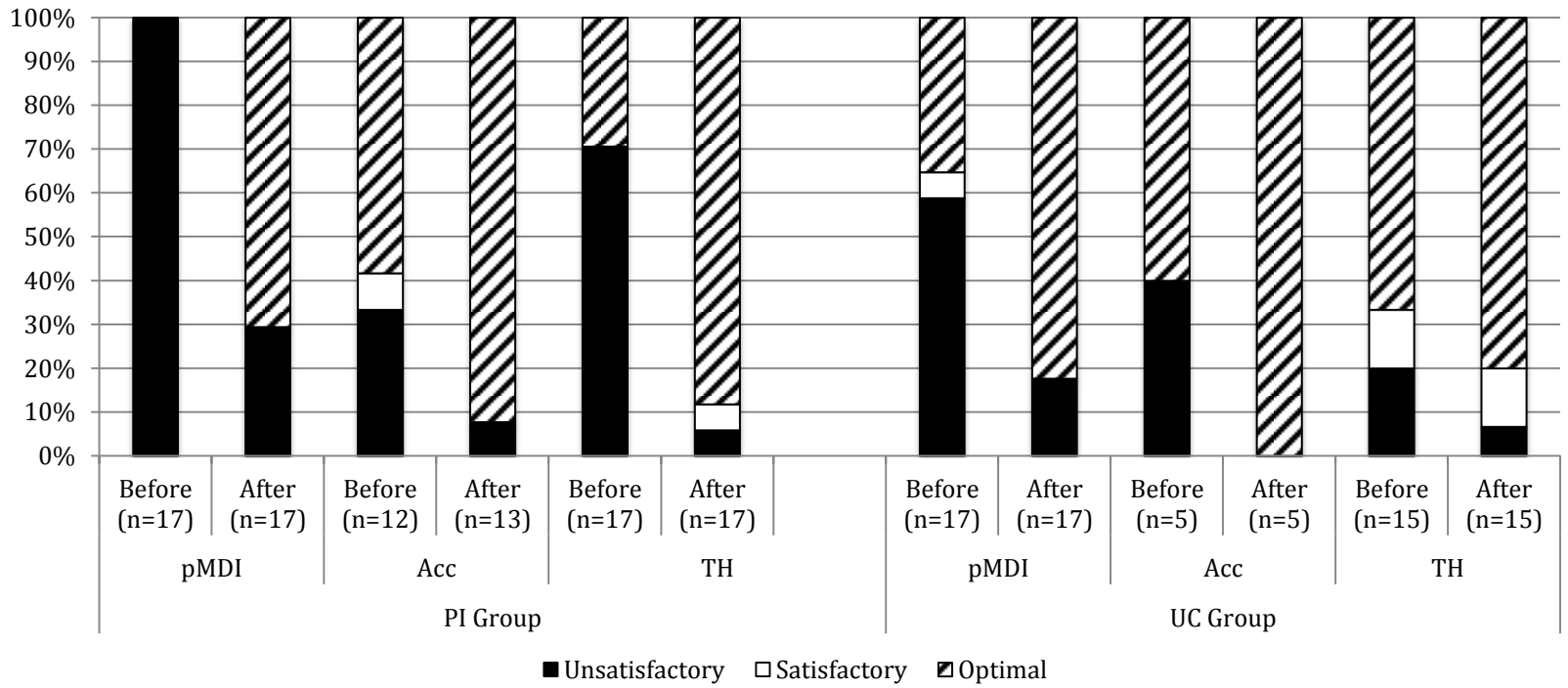


Figure 9. Effect of education on the proportion of patients with optimal, satisfactory, or unsatisfactory inhaler technique at baseline for the three most commonly used inhaler devices.

(Data for all inhaler devices are presented in **Figure 21, Appendix 15**). Optimal technique is defined as no errors using inhaler device; satisfactory inhaler technique is defined as making some minor but no critical errors; unsatisfactory inhaler technique is defined as making at least one critical error. PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler.

Table 9. Inhaler preference using previously published scoring methods (Lenney et al., 2000).

	Order of Preference			Total Score	Rank
	First	Second	Third		
Easi-Breathe	4	6	6	30	1
pMDI	6	3	3	27	2=
Turbohaler	5	3	6	27	2=
Accuhaler	4	4	2	22	4
Respimat	4	1	4	18	5
HandiHaler	3	3	1	16	6=
Easyhaler	0	6	4	16	6=

Table 10. Inhaler preference using alternative preference scoring system.

	Order of Preference							Total Score	Rank
	First	Second	Third	Fourth	Fifth	Sixth	Seventh		
Easi-Breathe	4	6	6	0	5	1	4	115	1
Turbohaler	5	3	6	3	3	3	3	113	2
pMDI	6	3	3	3	5	3	3	111	3
Accuhaler	4	4	2	5	4	3	4	104	4
Easyhaler	0	6	4	8	2	3	2	102	5
Respimat	4	1	4	3	3	7	3	92	6
HandiHaler	3	3	1	4	4	5	6	88	7

5.3.3 Targeted MURs

All 26 patients recruited to the PI group were referred to their community pharmacy for a t-MUR, but only six (23%) actually received one, at a mean 60 days (range 28 – 143 days) following randomisation. In addition, one patient in the UC group received a MUR 178 days after randomisation, despite both the patient and community pharmacist being requested verbally and in writing not to provide one during the study.

Explanations from community pharmacists and patients for the protocol deviation contrasted considerably. The community pharmacist admitted not arranging a t-MUR on four occasions, in one case because they claimed not to have received a written referral form. Eleven community pharmacists blamed the patient, either for not attending (10 occasions) or for not asking for a t-MUR (one occasion). Seven community pharmacists were unable to explain the protocol deviation. In contrast, patients blamed their community pharmacist for the lack of t-MUR, with 11 stating that their pharmacist did not arrange a t-MUR and one that the community pharmacist declined to perform a t-MUR stating that “that they couldn't do anything more than the pharmacist in the asthma

clinic". Four patients admitted fault, explained that they had insufficient time to attend, forgot, were unwell, or were unsure how to request a t-MUR. Two patients were unable to explain the failure to have a t-MUR.

The six patients in the PI group who received a t-MUR received a total of 11 interventions, comprising reinforcement of correct inhaler technique (n=4), education on medication or adherence (n=3), healthy living advice (n=2), and management of side effects (n=2). The one patient in the UC group who had a t-MUR received education on their medication.

5.4 Effect of pharmacist interventions on asthma control

5.4.1 Asthma control questionnaire

The primary outcome measure in the study was improvement in asthma control as measured using ACQ (Juniper et al., 1999b). The effect of pharmaceutical care in the PI group was found to be non-inferior to medical management in the UC group. At six months, the median (IQ) ACQ score had reduced from 2.86 (2.25, 3.25) and 3.00 (1.96, 3.71) in the PI and UC groups respectively to 2.57 (1.75, 3.67) and 2.29 (1.50, 3.50). This reflects a small improvement in asthma control (**Figure 10**), but this was not clinically or statistically significant in either the PI (Wilcoxon -0.870, p=0.931) or UC groups (Wilcoxon -1.150, p=0.250).

There was no difference between the two groups in the proportion of participants who had controlled asthma (defined as an ACQ <1.0 (Juniper et al., 2006)) at either baseline or follow-up. At baseline, one patient in each study group had controlled asthma (χ^2 0.000, p=1.000; Fisher's Exact Test), and at follow up, 1 participant in the PI group and 2 in the UC group had controlled asthma (χ^2 0.517, p=0.592; Fisher's Exact Test).

ACQ data at both baseline and follow-up were available for 45 participants. Eight and 13 patients in the PI and UC groups respectively experienced a *reduced* ACQ (*improved* asthma control), whilst 13 and six patients respectively experienced a raised ACQ (worsening asthma control), but this was not statistically significant (χ^2 3.786, p=0.151). Of these patients, four in each group achieved a clinically important improvement in asthma control (defined as a

reduction in ACQ >0.5 points), whilst four in the PI group and three in the UC group experienced a clinically important worsening in asthma control (χ^2 0.077, p=0.962).

Sub-group analysis for the six participants in the PI group who had a t-MUR showed that they did not have a significantly different asthma control than those who did not receive a t-MUR at baseline or at 6-month follow-up.

5.4.2 Other markers of asthma control

Participants in both the PI and UC groups required fewer corticosteroid rescue courses and used fewer doses of SABA reliever inhaler each week at follow up compared to baseline, however there was no significant difference between the two treatment arms at either baseline or follow-up (**Table 11**).

Reductions in FeNO were observed in both groups, but values were not statistically significant between groups. Lung function measures were stable throughout the study, and hospital admissions and A&E visits remained uncommon (**Table 11**).

There was no significant effect on median (IQ) equivalent beclometasone-CFC daily dose in either the PI (from 1600 (800, 2000) to 1800 (1150, 2000) micrograms) or UC groups (from 2000 (800, 2000) to 1600 (800, 2000) micrograms). Smoking status remained stable with three current smokers in the PI group at baseline and 6 months, compared to three at baseline and four at 6 months in the UC group.

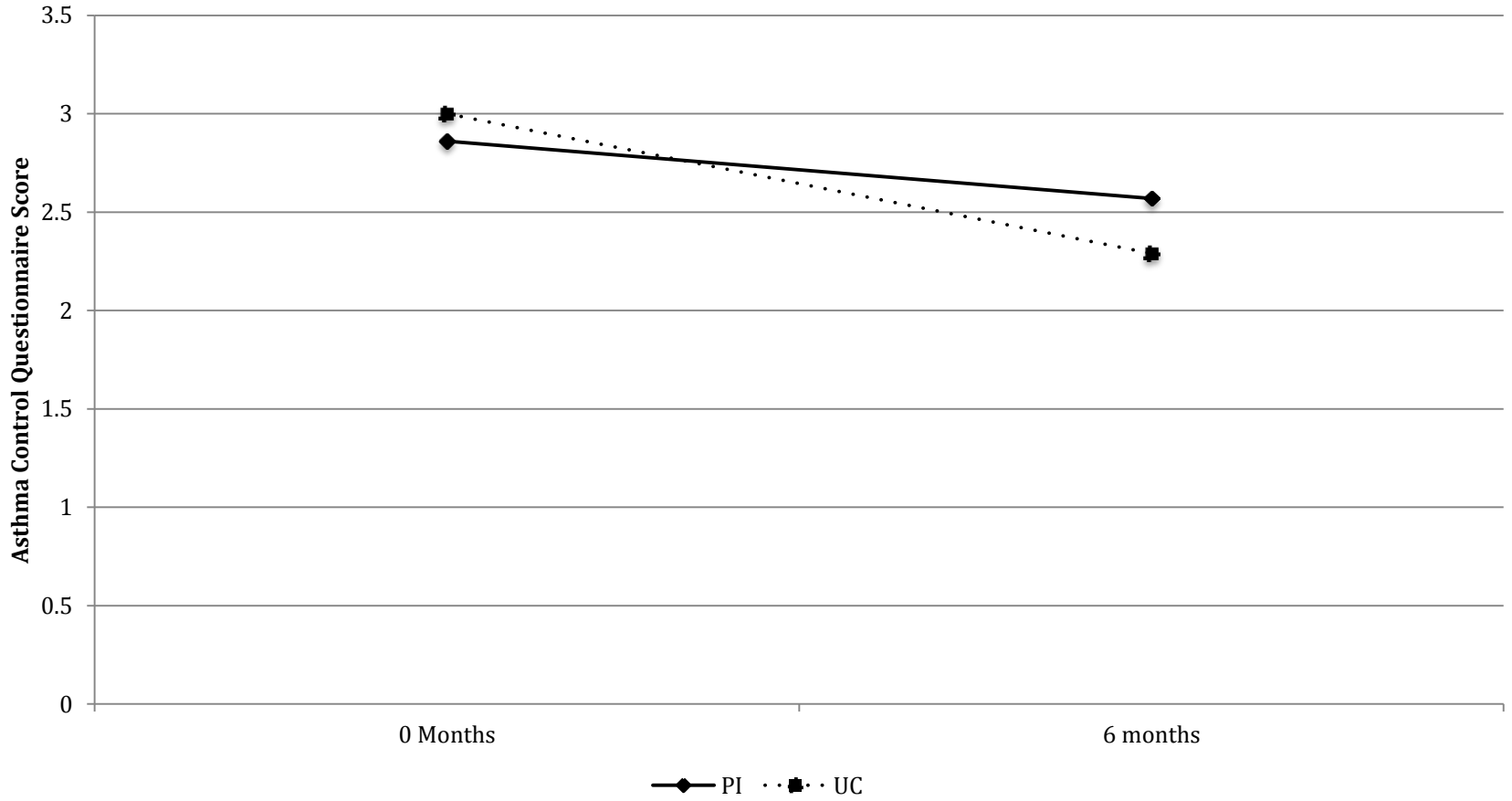


Figure 10. Change in median asthma control questionnaire score during study.

PI, pharmacist intervention group; UC, usual care group.

Table 11. Effects of interventions on measures of asthma control.

Outcome Measure	Intervention Arm	0 Months (n=52)	Difference between PI and UC groups at baseline		6 Months (n=45)	Difference between PI and UC groups at follow-up	
			Mann-Whitney	p value		Mann- Whitney	p value
ACQ (median, IQ)	PI	2.86 (2.25, 3.25)	333.000	0.927	2.57 (1.75, 3.67)	219.000	0.452
	UC	3.00 (1.96, 3.71)			2.29 (1.50, 3.50)		
Exhaled Nitric Oxide (median, IQ)	PI	38.0 (19.0, 70.75)	110.000	0.693	29.0 (14.0, 58.0)	140.500	0.707
	UC	27.0 (14.0, 67.0)			19.5 (14.0, 55.25)		
% Predicted FEV_1 (mean (SD))	PI	72.92 (20.06)	0.432*	0.668	69.59 (20.02)	-0.575*	0.568
	UC	70.57 (18.41)			72.61 (15.07)		
FEV_1/FVC (mean (SD))	PI	69.46 (11.05)	0.079*	0.937	67.12 (13.31)	-0.890*	0.378
	UC	69.21 (10.61)			70.19 (9.68)		
Steroid courses in previous 3 months (median, IQ)	PI	2.0 (1.0, 3.0)	266.500	0.179	0.0 (0.0, 2.0)	256.500	0.857
	UC	1.0 (0.0, 2.0)			0.0 (0.0, 2.0)		
Hospital admissions in previous 3 Months (median, IQ)	PI	0.0 (0.0, 1.0)	327.000	0.819	0.0 (0.0, 0.0)	232.500	0.194
	UC	0.0 (0.0, 1.0)			0.0 (0.0, 1.0)		
Number of puffs of SABA per week (median, IQ)	PI	49.0 (33.25, 64.75)	328.000	0.854	42.0 (15.75, 56.0)	275.000	0.983
	UC	45.5 (12.5, 90.5)			35.0 (28.0, 63.0)		

PI, pharmacist intervention group; UC, usual care group; ACQ, asthma control questionnaire score; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IQ, interquartiles; SD, standard deviation; *, independent Samples T test used.

Table 12. Effect of interventions on asthma quality of life measures.

Outcome Measure	Intervention Arm	0 Months (n=52)	Difference between PI and UC groups at baseline		6 Months (n=47)	Difference between PI and UC groups at follow-up	
			Mann-Whitney	p value		Mann-Whitney	p value
AQLQ(S) (median, IQs)	PI	4.11 (3.38, 5.21)	310.500	0.615	4.12 (3.55, 5.49)	269.000	0.882
	UC	3.77 (2.87, 5.30)			4.22 (2.97, 5.66)		
• AQLQ-Symptoms (median, IQs)	PI	3.75 (2.89, 5.73)	322.000	0.770	4.00 (3.42, 5.27)	266.000	0.831
	UC	3.67 (3.06, 5.13)			4.17 (2.92, 5.58)		
• AQLQ-Activity Limitations (median, IQs)	PI	4.41 (3.64, 5.52)	290.000	0.379	4.50 (3.48, 5.91)	247.500	0.544
	UC	4.23 (2.91, 5.89)			4.47 (2.91, 6.36)		
• AQLQ-Emotional Function (median, IQs)	PI	3.90 (2.80, 5.10)	296.500	0.447	3.80 (3.00, 5.10)	242.000	0.468
	UC	4.20 (3.10, 5.50)			4.60 (3.20, 5.40)		
• AQLQ-Environmental Stimuli (median, IQs)	PI	4.50 (3.69, 5.25)	300.000	0.486	4.63 (3.75, 5.69)	238.500	0.424
	UC	4.25 (3.00, 6.63)			4.25 (3.00, 6.00)		

PI, pharmacist intervention group; UC, usual care group; AQLQ(S), standardised asthma quality of life questionnaire; IQ, interquartiles.

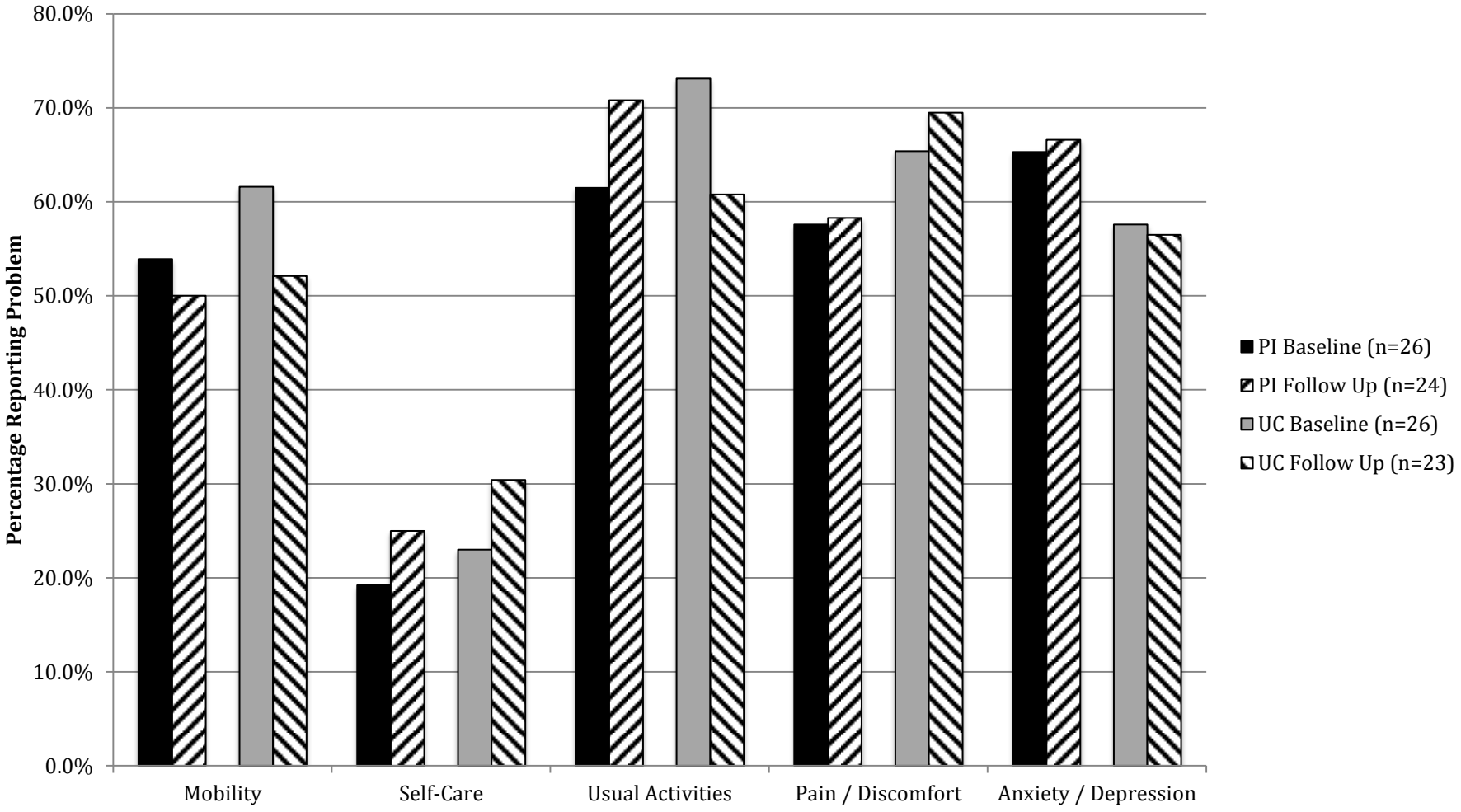


Figure 11. Profile of the population (%) reporting problem, using EQ-5D-5L questionnaire.

PI, pharmacist intervention group; UC, usual care group.

5.5 Quality of life

5.5.1 Asthma quality of life

At six-months, the effect of pharmaceutical care in the PI group on asthma quality of life, using Juniper's standardised asthma quality of life questionnaire (AQLQ(S)) (Juniper et al., 1999a), was found to be non-inferior to medical management in the UC group. Similarly pharmacist management was non-inferior to usual medical care in all four individual domains of the AQLQ(S), including symptoms, activity limitation, emotional function and environmental stimuli (**Table 12**).

On average, participants in both groups reported to be very limited or have moderate limitation in their quality of life and within all domains, at both baseline and follow-up. At baseline, the median (IQ) AQLQ(S) score was 4.11 (3.38, 5.21) and 3.77 (2.87, 5.30) in the PI and UC groups respectively, and at follow-up was 4.12 (3.55, 5.49) and 4.22 (2.97, 5.66) respectively, and was not statistically different between the two groups at either baseline (Mann-Whitney 310.5, p=0.615) or follow-up (Mann-Whitney 269.0, p=0.882).

Of the 47 participants who completed the study and had baseline and follow-up data available, an improvement in AQLQ(S) was found in 11 and 14 participants in the PI and UC group respectively, whilst a worsening was found in 12 and 8 participants respectively. There was no significant difference between the two study groups (χ^2 1.139, p=0.566). A clinically important improvement in quality of life (defined as an increase in AQLQ(S) score of >0.5 units) was found in six and five participants in the PI and UC groups respectively, whilst a clinically important worsening in quality of life (decrease in AQLQ(S) score of >0.5 units) was found in three participants in each group. There was no significant difference between the two study groups (χ^2 0.070, p=0.966).

Sub-group analysis of participants in the PI group who had a t-MUR did not demonstrate any significant effect of quality of life compared to those who did not have a t-MUR.

5.5.2 General health status

Health status, as measured using the EQ-5D-5L questionnaire demonstrated no differences in the proportion of participants in the PI and UC groups reporting problems within each of the five dimensions of the questionnaire (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) at either baseline or at follow-up using Chi-Square analysis. At six months, a small decrease in the proportion of participants reporting problems with mobility was observed in both groups, but slightly more participants reported problems with pain and self-care. In contrast, whilst there were small increases in the proportion of participants reporting problems with usual activities and anxiety/depression in the PI group, the opposite was observed in the UC group (**Figure 11**).

The mean self-rated health status, as measured using the EQ VAS was similar at baseline in both study groups (**Table 13**), and improved similarly over 6-months in both study groups, but was not statistically significant (mean (SD) increase in EQ VAS was 1.88 (19.43) and 3.89 (15.38) in the PI and UC groups respectively; independent samples test -0.0396, p=0.694).

Table 13. EQ VAS values.

	PI		UC	
	0 Months (n=26)	**6 Months (n=24)**	**0 Months (n=25)**	**6 months (n=23)**
Mean	60.96	62.72	63.48	66.59
SD	16.972	19.866	17.093	13.979

PI pharmacist intervention group; UC, usual care group; SD, standard deviation.

5.6 Inhaler technique

5.6.1 Inspiratory flow

Inhaler technique education during the baseline consultation improved the IFR though different devices amongst participants in the PI group, in particular for those using the pMDI device, and also increased the number of patients who achieved the correct IFR. Six-months after the intervention, there was a large clinically important and statistically significant increase in the median (IQ) peak IFR through pMDI devices of 35.0 (21.3, 85.0) L/min (Wilcoxon -3.413, p=0.001) in the PI group and 80.0 (20.0, 107.5) L/min (Wilcoxon -2.971, p=0.003) in the UC group. There was a similarly large increase in the peak IFR through Easi-

Breathe inhalers from a median of 50 and 70 L/min to 55 and 92.5 L/min in the PI and UC groups respectively, but did not reach statistical significance (Wilcoxon -0.447, P=0.655 and Wilcoxon -1.342, p=0.180 respectively) due to low numbers of participants using these devices. In addition, there was also a small, but statistically significant, reduction in the median peak IFR through Turbohaler devices -5.0 (-21.3, 0.0) L/min (Wilcoxon -2.002, p=0.045) and -7.5 (-20.0, 1.3) L/min (Wilcoxon -2.175, p=0.030) in the PI and UC groups respectively. There was no significant change in the peak IFR over 6-months for participants in the PI group using Accuhaler or HandiHaler devices, but in the UC group there was a large increase in the median IFR through Accuhaler devices of 42.5 (5.0, 65.0) L/min (Wilcoxon -1.461, p=-0.144), which was not statistically significant due to low patient numbers using this device (**Figure 12**).

These changes in IFR over the 6-month study duration was clinically important for pMDI devices, since was associated with a large reduction in the number of patients who were using this inhaler at the correct IFR (from 15 to 2 participants in the PI group and from 10 to 3 participants in the UC group). The observed increases in IFR through dry powder devices had no impact on the number of participants using these inhaler devices at the correct IFR (**Figure 13**).

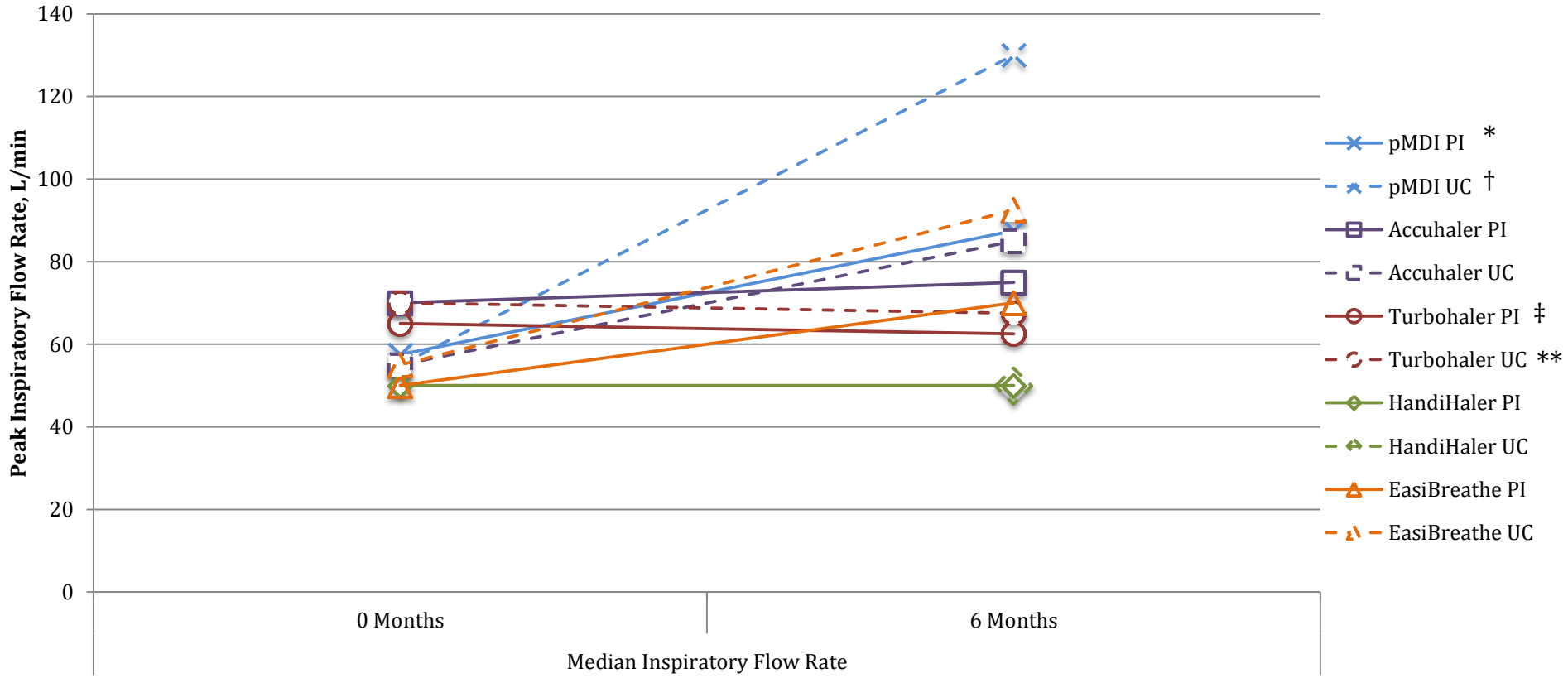


Figure 12. Change in median peak inspiratory flow rate through inhaler devices.

PI, pharmacist intervention group (bold lines); UC, usual care group (dashed lines); pMDI, pressurised metered dose inhaler (target inspiratory flow 25-60 L/min); Accuhaler (target inspiratory flow 30-90 L/min); Turbohaler (target inspiratory flow 30-90 L/min); HandiHaler (target inspiratory flow 20-60 L/min); Easi-Breathe (target inspiratory flow 20-60 L/min). Change in peak IFR between baseline and 6-month follow-up; *pMDI PI p=0.001; †pMDI UC p=0.003; ‡Turbohaler PI p=0.045; **Turbohaler UC p=0.030

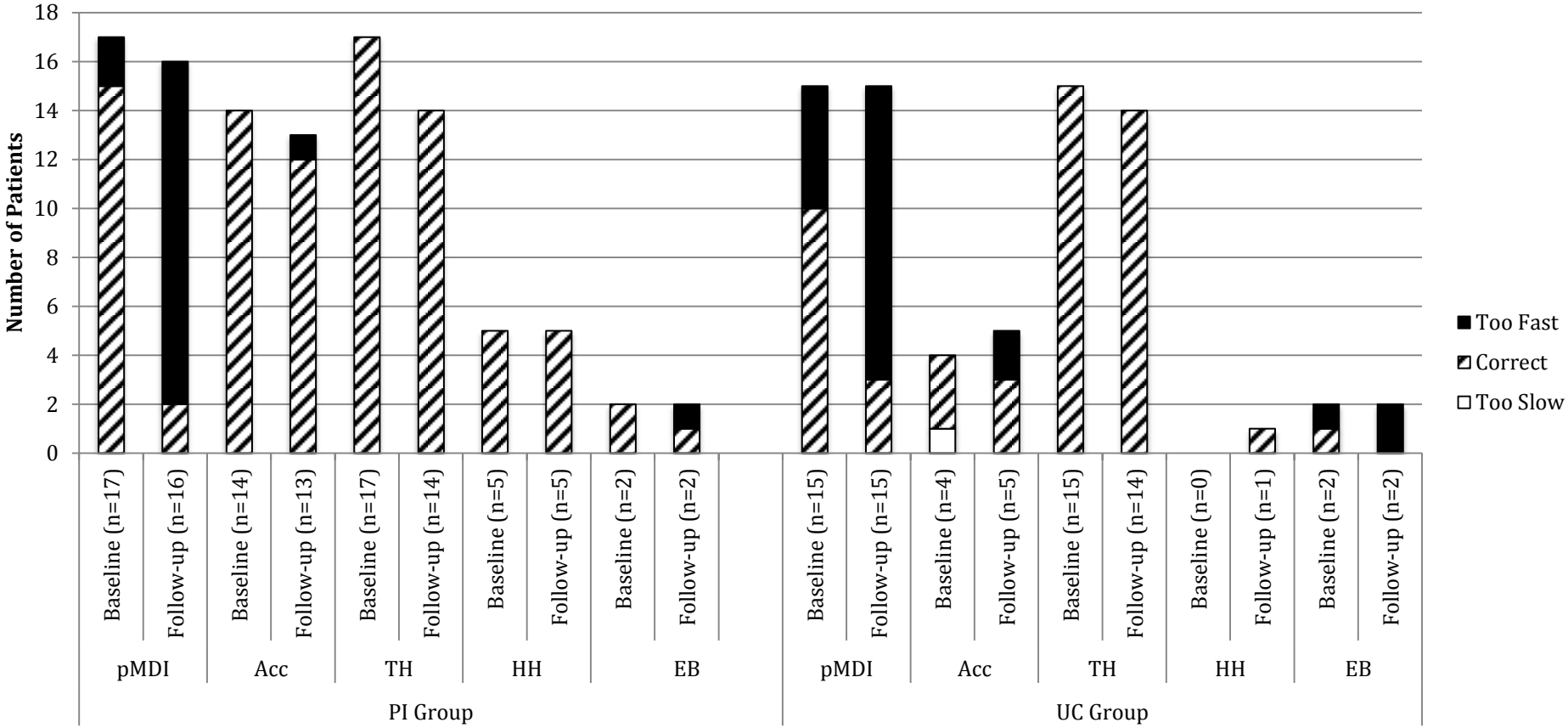


Figure 13. Effect of the intervention on the number of patients maintaining correct peak inspiratory flow rate through inhaler devices.

PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; HH; HandiHaler; EB, Easi-Breathe.

5.6.2 Inhaler technique score

Although inhaler technique (calculated as the percentage of all steps completed correctly) improved with education at the baseline consultation, this was not maintained during the 6-month study for all inhaler devices (**Figure 14**). In particular, the mean (SD) inhaler technique score was significantly worse for pMDI at 6-months compared to the baseline score after education for participants in both the PI and UC groups (-9.09% (8.13); Wilcoxon -3.025, p=0.002, and -9.09% (15.68); Wilcoxon -2.032, p=0.042 respectively), and for Turbohaler device in UC patients (-5.71% (7.56); Wilcoxon -2.309, p=0.021). Inhaler technique scores at 6 months were higher for dry powder inhalers than for aerosol inhalers. The highest mean (SD) scores were observed in participants using Turbohaler devices (95.38% (7.76) and 92.86% (7.26) in the PI and UC groups respectively), followed by Accuhaler devices (94.02% (13.31) and 91.11% (12.17) in the PI and UC groups respectively). The mean (SD) score for pMDI devices was lower at 88.24% (6.24) and 83.77% (10.20) respectively (**Table 14**).

Participants in the PI group who had a t-MUR and reinforcement of inhaler technique did not have a significantly different inhaler technique score from participants in the UC group, indicating no additive benefit from the t-MUR.

5.6.3 Classification of inhaler technique

The proportion of patients with optimal inhaler technique at baseline was poor for all devices prescribed to individual participants, but education during the initial consultation resulted in the majority achieving optimal technique. At two and six months, the proportion of participants with optimal inhaler technique was not maintained (**Figure 15**). This was particularly so for the three most commonly prescribed inhaler devices: pMDI, Accuhaler and Turbohaler. In these cases the initial percentage of participants with optimal inhaler technique increased with education at the baseline consultation from 0% to 70.6%, 58.3% to 92.3% and 29.4% to 88.2% respectively. At 2-months, in those patients who had a t-MUR, there were 0% and 25% who had optimal inhaler technique with pMDI and Turbohaler devices. At six months, the percentage of patients with optimal inhaler technique was 6.3%, 75% and 71.4% for pMDI, Accuhaler and Turbohaler devices (**Table 15**). At 6-months, there was no statistically

significant difference in the proportion of participants in the PI and UC group who had optimal inhaler technique for pMDI (χ^2 0.010, p=1.000; Fisher's Exact Test), Accuhaler (χ^2 0.383, p=0.600; Fisher's Exact Test) or Turbohaler (χ^2 2.333, p=0.252; Fisher's Exact Test).

Similar to the inhaler technique score, sub-group analysis did not demonstrate any significant effect on the proportion of participants with optimal inhaler technique after having a t-MUR.

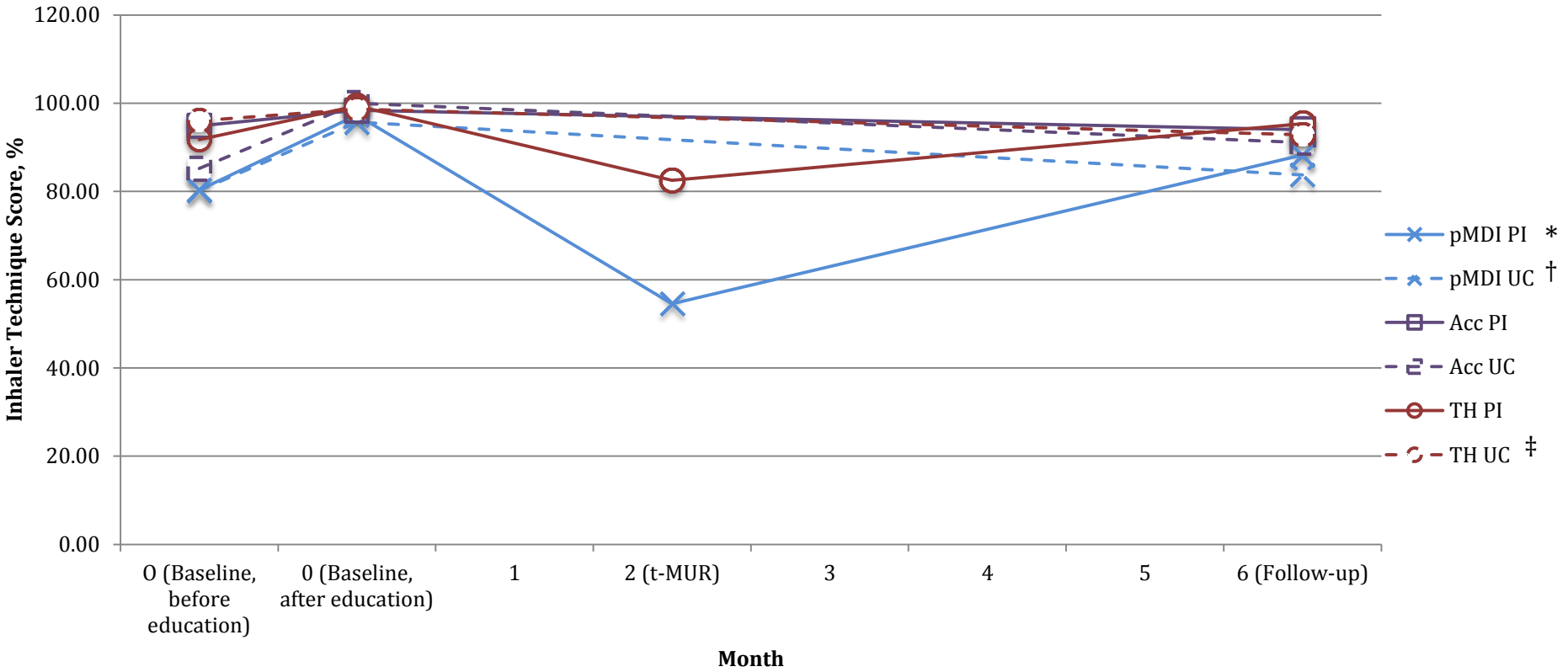


Figure 14. Effect of education on inhaler technique score (% of each step performed correctly) throughout study, for the three most commonly used inhaler devices.

(Data for all inhaler devices are presented in **Figure 22, Appendix 16**). PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler. Improvements in inhaler technique assessed using Wilcoxon test. Change in inhaler technique score from baseline to six-month follow-up: *pMDI PI p=0.002; †pMDI UC p=0.042; ‡TH UC p=0.021

Table 14. Effect of education on inhaler technique score (% of each step performed correctly) throughout study.

Inhaler Device	Intervention Arm	0 Months (before education)		0 Months (after education)		2 Months (t-MUR)		6 Months (Follow-up)	
		n	% (SD) Score	n	% (SD) Score	n	% (SD) Score	n	% (SD) Score
pMDI	PI	17	80.30 (7.38)	17	97.33 (4.27)	2	54.55 (51.43)	17	88.24 (6.24) *
	UC	17	80.21 (24.32)	17	95.72 (10.22)	0	n/a	14	83.77 (10.20) †
Acc	PI	13	94.87 (7.34)	14	98.41 (5.94)	0	n/a	13	94.02 (13.31)
	UC	5	82.22 (25.58)	5	100.00 (0.00)	0	n/a	5	91.11 (12.17)
TH	PI	17	91.76 (6.36)	17	99.41 (2.43)	4	82.50 (17.08)	13	95.38 (7.76)
	UC	15	96.00 (6.32)	15	98.67 (3.52)	0	n/a	14	92.86 (7.26) ‡
HH	PI	4	94.23 (7.36)	4	96.92 (6.88)	2	76.93 (21.76)	5	98.46 (3.44)
	UC	1	84.62	1	100	0	n/a	1	92.31
EB	PI	2	83.34 (7.86)	2	94.45 (7.86)	1	88.89	2	94.45 (7.86)
	UC	2	94.45 (7.86)	2	94.45 (7.86)	0	n/a	2	83.34 (7.86)
EH	PI	1	100.00	3	93.33 (5.77)	1	90	2	90.00 (14.14)
	UC	0	n/a	0	n/a	0	n/a	0	n/a
MDISS	PI	2	92.86 (0.00)	2	100.00 (0.00)	1	85.71	1	100
	UC	0	n/a	0	n/a	0	n/a	0	n/a
MDISM	PI	1	85.71	1	100	1	92.86	2	100.00 (0.00)
	UC	1	100.00	1	100	0	n/a	1	78.57
RSP	PI	0	n/a	0	n/a	0	n/a	0	n/a
	UC	2	40.00 (28.28)	2	40.00 (28.28)	0	n/a	1	100

PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; HH; HandiHaler; EB, Easi-Breathe; EH, Easyhaler; MDISS, pMDI + spacer (single-breath method); MDISM, pMDI + spacer (multiple-breath method); RSP, Respimat. *,p=0.002 vs. 0 months (after education); †, p=0.042 vs. 0 months (after education); ‡, p=0.021 vs. 0 months (after education).Improvements in inhaler technique assessed using Wilcoxon test.

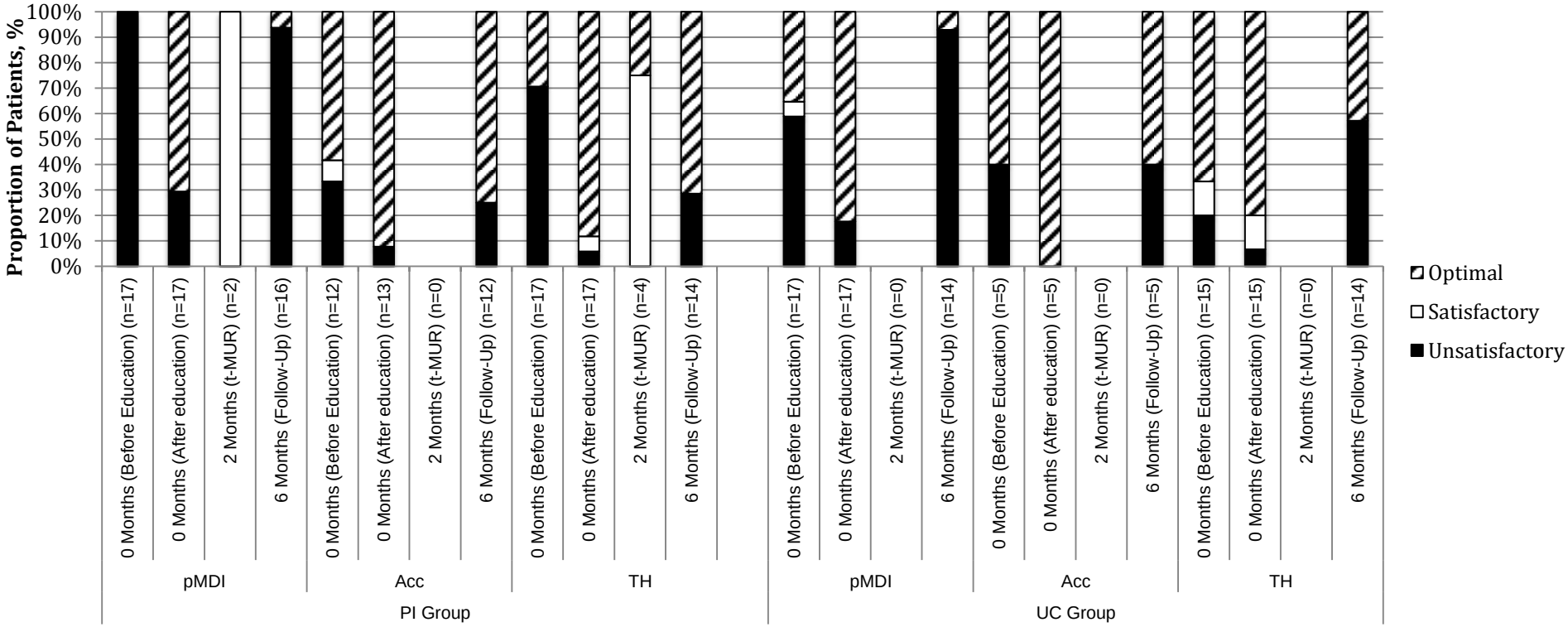


Figure 15. The proportion of patients with optimal, satisfactory, or unsatisfactory inhaler technique throughout the 6-month study, for the three most commonly used inhaler devices.

(Data for all inhaler devices are presented in **Figure 23, Appendix 17**). Optimal technique is defined as no errors using inhaler device; satisfactory inhaler technique is defined as making some minor bur no critical errors; unsatisfactory inhaler technique is defined as making at least one critical error. PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler.

Table 15. The number of patients with optimal, satisfactory, or unsatisfactory inhaler technique throughout the 6-month study

Treatment Arm	Device	Time	Number of Participants Assessed	Unsatisfactory Inhaler Technique		Satisfactory Inhaler Technique		Optimal Inhaler Technique	
				n	%	n	%	n	%
PI	pMDI	0 Months (Before Education)	17	17	100.0%	0	0.0%	0	0.0%
		0 Months (After education)	17	5	29.4%	0	0.0%	12	70.6%
		2 Months (t-MUR)	2	0	0.0%	2	100.0%	0	0.0%
		6 Months (Follow-Up)	16	15	93.8%	0	0.0%	1	6.3%
	Accuhaler	0 Months (Before Education)	12	4	33.3%	1	8.3%	7	58.3%
		0 Months (After education)	13	1	7.7%	0	0.0%	12	92.3%
		2 Months (t-MUR)	0	0	n/a	0	n/a	0	n/a
		6 Months (Follow-Up)	12	3	25.0%	0	0.0%	9	75.0%
	Turbohaler	0 Months (Before Education)	17	12	70.6%	0	0.0%	5	29.4%
		0 Months (After education)	17	1	5.9%	1	5.9%	15	88.2%
		2 Months (t-MUR)	4	0	0.0%	3	75.0%	1	25.0%
		6 Months (Follow-Up)	14	4	28.6%	0	0.0%	10	71.4%
UC	pMDI	0 Months (Before Education)	17	10	58.8%	1	5.9%	6	35.3%
		0 Months (After education)	17	3	17.6%	0	0.0%	14	82.4%
		2 Months (t-MUR)	0	0	n/a	0	n/a	0	n/a
		6 Months (Follow-Up)	14	13	92.9%	0	0.0%	1	7.1%
	Accuhaler	0 Months (Before Education)	5	2	40.0%	0	0.0%	3	60.0%
		0 Months (After education)	5	0	0.0%	0	0.0%	5	100.0%
		2 Months (t-MUR)	0	0	n/a	0	n/a	0	n/a
		6 Months (Follow-Up)	5	2	40.0%	0	0.0%	3	60.0%
	Turbohaler	0 Months (Before Education)	15	3	20.0%	2	13.3%	10	66.7%
		0 Months (After education)	15	1	6.7%	2	13.3%	12	80.0%
		2 Months (t-MUR)	0	0	n/a	0	n/a	0	n/a
		6 Months (Follow-Up)	14	8	57.1%	0	0.0%	6	42.9%

Optimal technique is defined as no errors using inhaler device; satisfactory inhaler technique is defined as making some minor bur no critical errors; unsatisfactory inhaler technique is defined as making at least one critical error. PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; EB, Easi-Breathe; EH, Easyhaler; HH; HandiHaler; RSP, Respimat; MDISM, pMDI + spacer (multiple-breath method); MDISS, pMDI + spacer (single-breath method).

5.7 Adherence

5.7.1 Patient reported adherence compared to prescription data

Four patients in the PI group self-reported poor adherence, whilst all other patients in the PI and UC groups reported no problems with adherence, but this was not supported by prescription data from GP and hospital records.

Based on analysis of prescription data for 40 participants where this was available over a six-month period prior to randomisation, median (IQ) adherence rate to ICS (defined as the percentage of prescribed doses issued compared to expected prescribed number of doses required over a six-month period) was 75.30% (35.71, 98.51), and ranged from 5% to 600%. This was not significantly different between the two study arms. 57.5% of patients had adherence rates less than 80%, 35% had adherence rates less than 50%. 17.5% of participants had adherence rates exceeding 100%, of whom 6 (15%) had adherence rates exceeding 120% (**Figure 16**).

Although the proportion of patients with adherence rates 80-100% increased in the PI group compared to the UC group, this was not significantly different at either baseline (6/19 and 4/21 participants respectively; χ^2 0.835, p=0.473; Fisher's Exact Test), or at the 6-month follow-up visit (8/20 and 3/21 participants respectively; χ^2 3.450, p=0.085; Fisher's Exact Test). However specifying an upper limit of 100% may inappropriately suggest that some patients have been overusing their medicines, as some may have been proactive and obtained a repeat prescription early to prevent missed doses, such as to cover holidays. Consequently it may be appropriate to define good adherence as an adherence rate of 80-120% as this will include patients who may have received a prescription early, whilst excluding those who may be overusing their inhalers and have a very high adherence rate. Furthermore, previous pharmacist intervention studies have classified adherent patients as those taking 80-120% of preventer medication prescribed, although without explanation or discussion for this (Armour et al., 2007). When adherence rates of 80-120% were considered, a significantly greater proportion of participants in the PI group were classed as adherent at the 6-month follow-up visit compared to the UC group (10/20 vs. 3/21; χ^2 6.034, p=0.020; Fisher's Exact Test χ^2).

5.7.2 Medication Adherence Report Scale (MARS)

Self-reported adherence to ICS, measured using the MARS questionnaire (Horne and Weinman, 2002) demonstrated that whilst the mean MARS scores were high indicating self-reported good adherence (ranging from 3.88 to 4.96 out of 5 for all questions), a relatively large percentage of patients admitted to some form of non-adherent behaviour (**Table 16**). Specifically, at baseline 46.2% and 26.9% of PI and UC participants admitted to altering the dose of their ICS, 42.3% and 26.9% respectively admitted to taking more than instructed, and 11.5% of UC participants admitted to stopping their ICS for a while (**Figure 17**).

This behaviour was not significantly different at the 6-month follow-up visit, with the exception that significantly more participants in the PI group admitted to stopping their ICS for a while (increased from a mean 0% to 12.5%; Wilcoxon -2.264, p=0.024).

5.7.3 Beliefs about Medicines Questionnaire (BMQ)

The BMQ data (**Table 17**) demonstrate that the participants in the study had high levels of perception of the necessity for taking their asthma medications, as indicated by high mean (SD) scores in the BMQ-Specific Necessity sub-scale (mean score 20.69 (3.56) amongst all participants). Although there were some concerns about taking medicines (BMQ-Specific Concerns sub-scale mean score of 17.80 (4.84) in all patients), this was not reflected by concerns of overuse or harm from medicines, as indicated by a BMQ-General-overuse sub-scale mean score 9.31 (2.64) and BMQ-General-harm sub-scale mean score of 9.52 (2.52) in all patients. There were very few people who reported high levels of concerns about asthma medicines, with only four, one and two participants reporting high levels of concerns in the BMQ-Specific Necessity, BMQ-General-overuse, and BMQ-General-harm sub-scales respectively at baseline.

There was no significant difference in beliefs about medicines between participants in the two intervention arms, nor were there any differences in medication beliefs at follow-up.

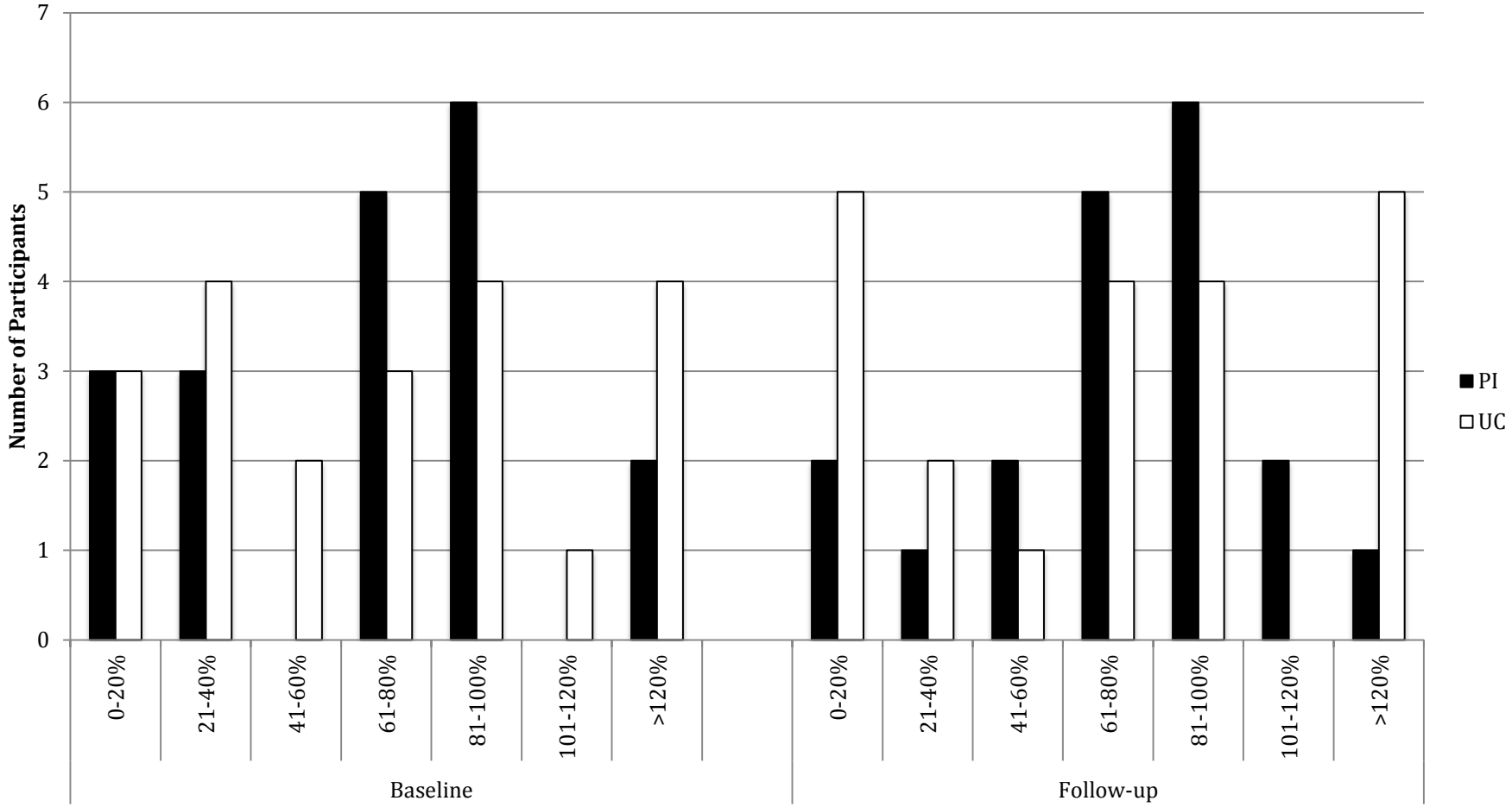


Figure 16. Frequency of six-month adherence rates to inhaled corticosteroid inhalers in participants In the PI and UC groups.

PI, pharmacist intervention group; UC, usual care group.

Table 16. Adherence to inhaled corticosteroid using MARS questionnaire.

	Type of non-adherent behaviour relating to ICS use	Baseline				Follow-up			
		Mean (SD) score (range 1-5) (High scores indicates self-reported good adherence)		Percentage of sample admitting to non-adherent behaviour		Mean (SD) score (range 1-5) (High scores indicates self-reported good adherence)		Percentage of sample admitting to non-adherent behaviour	
		PI	UC	PI	UC	PI	UC	PI	UC
M1	I forget to take them	4.31 (0.74)	4.35 (1.04)	15.4%	19.2%	4.42 (0.72)	4.32 (1.04)	12.5%	18.2%
M2	I alter the dose	3.92 (1.09)	4.27 (1.04)	46.2%	26.9%	4.08 (1.28)	4.14 (1.04)	25.0%	36.4%
M3	I stop taking them for a while	4.96 (0.20)	4.65 (0.69)	0.0%	11.5%	4.54 (0.98)	4.82 (0.59)	12.5%	9.1%
M4	I decide to miss out a dose	4.73 (0.60)	4.85 (0.46)	7.7%	3.8%	4.38 (1.25)	4.82 (0.40)	13.0%	0.0%
M5	I take less than instructed	4.96 (0.20)	4.81 (0.49)	0.0%	3.8%	4.71 (0.62)	4.82 (0.50)	8.3%	4.5%
M6	I take more than instructed	3.88 (1.40)	4.27 (1.04)	42.3%	26.9%	4.08 (1.21)	4.43 (0.99)	29.2%	17.4%

PI, pharmacist intervention group; UC, usual care group; SD, standard deviation.

Table 17. Beliefs about medicines questionnaire (BMQ) results.

BMQ Scale	Sub-scale	Baseline Mean (SD) score		Follow-up Mean (SD) score	
		PI	UC	PI	UC
BMQ-Specific	Necessity (range 5-25)	20.64 (2.56)	20.73 (4.36)	21.13 (3.10)	20.64 (3.42)
	Concerns (range 6-30)	18.64 (5.21)	17.00 (4.41)	18.00 (5.67)	16.78 (3.91)
BMQ-General	General-overuse (range 4-20)	9.48 (2.35)	9.15 (2.94)	9.46 (2.38)	7.96 (2.57)
	General-harm (range 4-20)	10.04 (2.74)	9.33 (2.65)	9.88 (2.19)	9.14 (2.83)

High scores in the BMQ necessity sub-scale indicates increased perception of necessity of medicines. High scores in the BMQ concerns, general-overuse and general-harm subscales indicate negative perceptions of medicines. PI, pharmacist intervention group; UC, usual care group.

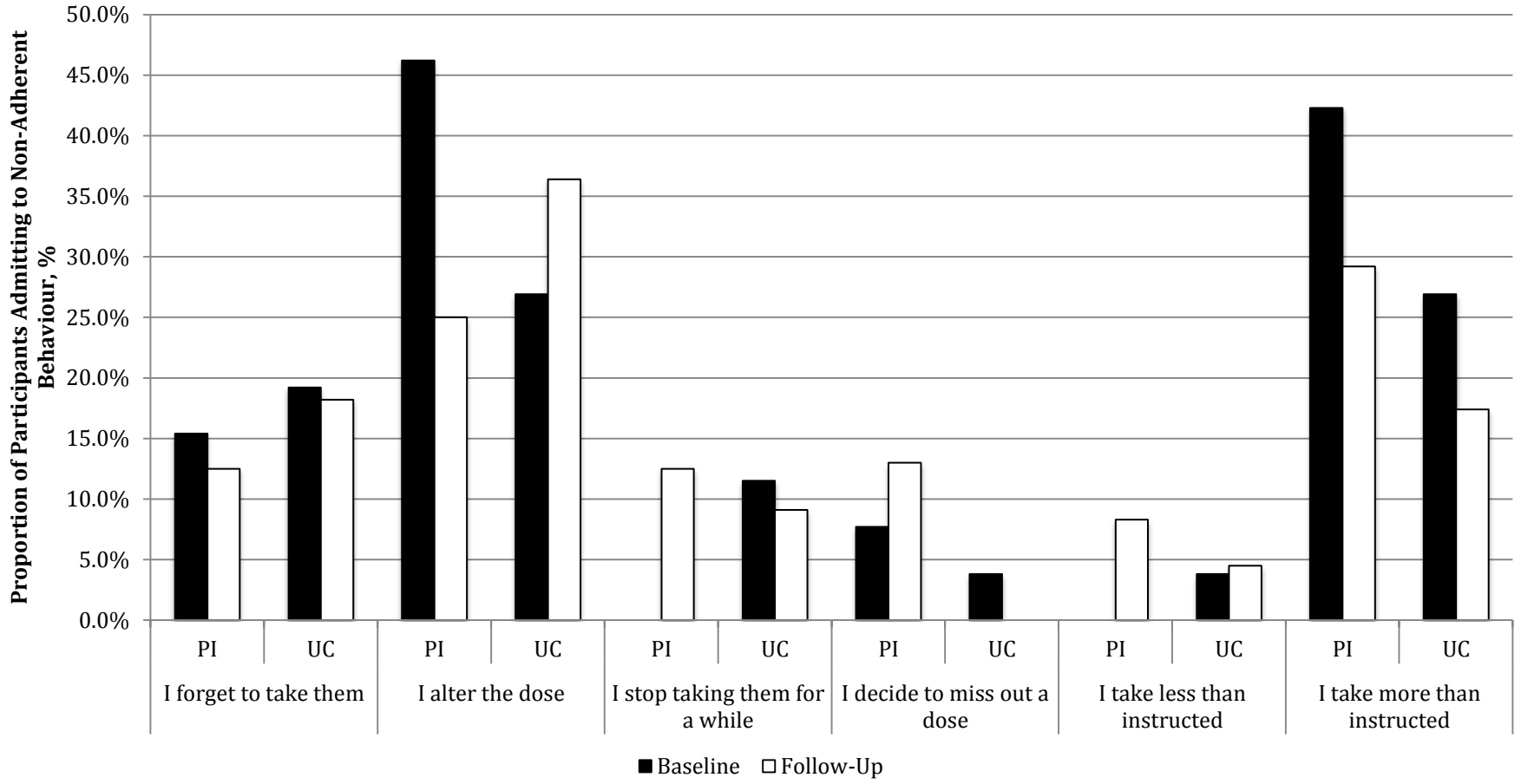


Figure 17. Proportion of participants admitting to non-adherent behaviours at baseline and a follow-up, using the self-administered MARS questionnaire.

PI, pharmacist intervention group; UC, usual care group.

5.8 Effect of adherence on asthma outcomes

As adherence was so variable amongst participants in both the PI and UC groups, an analysis was performed to examine whether there was an association between adherence to ICS and either asthma control or asthma quality of life. Since there was no significant difference between asthma control or quality of life in participants randomised to either the PI or UC group, the results for both study groups were combined for subsequent analyses. Adherence data were available for 36 participants who also had ACQ data at 6-months, and for 37 participants who also had AQLQ(S) data at 6-months.

Bivariate correlation found no significant relationship between adherence and either asthma control (Spearman's rho 0.188, p=0.271) or asthma quality of life (Spearman's rho 0.108, p=0.537) at six-months. Scatter plot graphs of adherence to maintenance ICS during the six-month study demonstrate clearly this lack of correlation with either asthma control, measured using ACQ (**Figure 18**), or quality of life, measured using AQLQ(S) (**Figure 19**) at 6-months, with the R Square statistic demonstrating that adherence may explain only 5.1% and 1.3% of the variability in ACQ and AQLQ(S) respectively.

There was no significant difference between the proportions of participants who had good adherence (defined as taking 80-120% of ICS doses) to those who were non-adherent to ICS who achieved improvements in asthma control (5/13 and 13/23 respectively; χ^2 1.926, p=0.382), or asthma quality of life (7/13 and 13/23 respectively; χ^2 0.581, p=0.748).

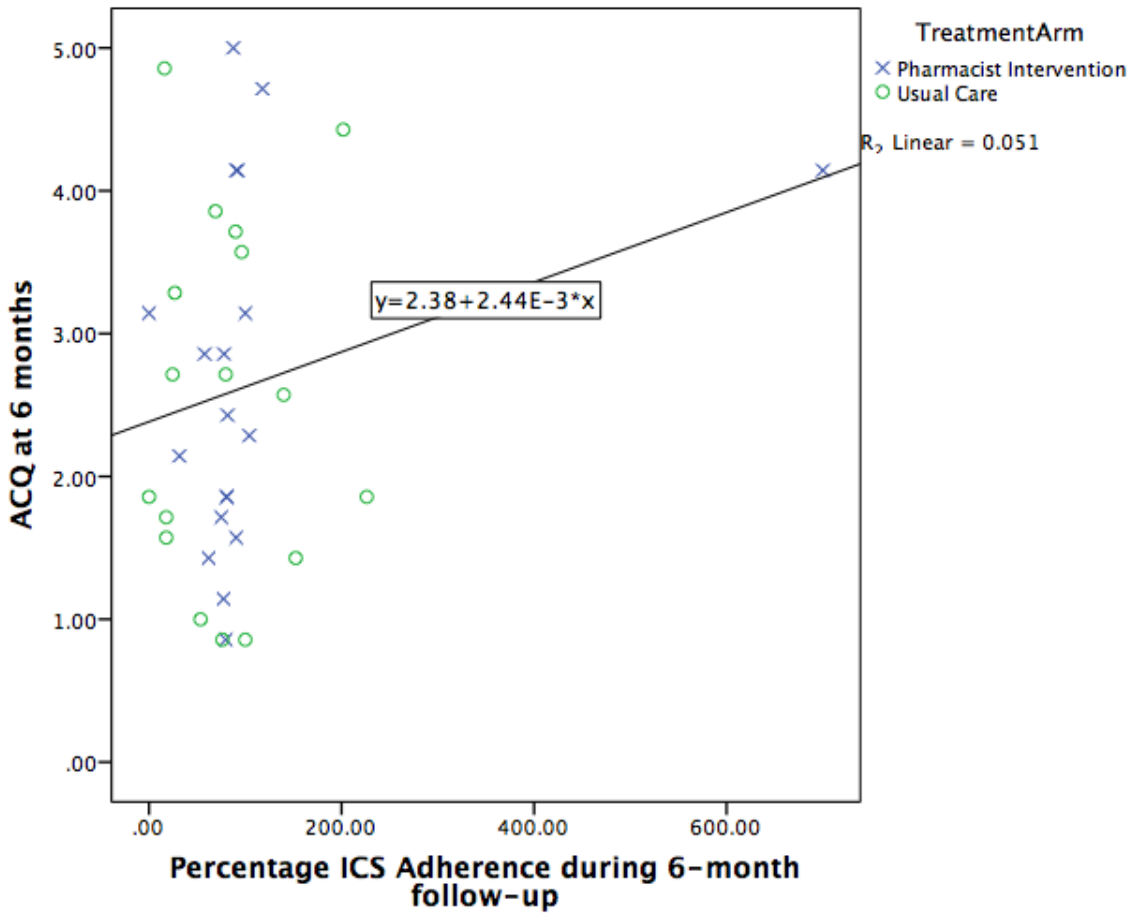


Figure 18. Scatter plot of adherence to ICS during the study and effect on asthma control, measured using ACQ at the end of the study.

ACQ, asthma control questionnaire; ICS, inhaled corticosteroid.

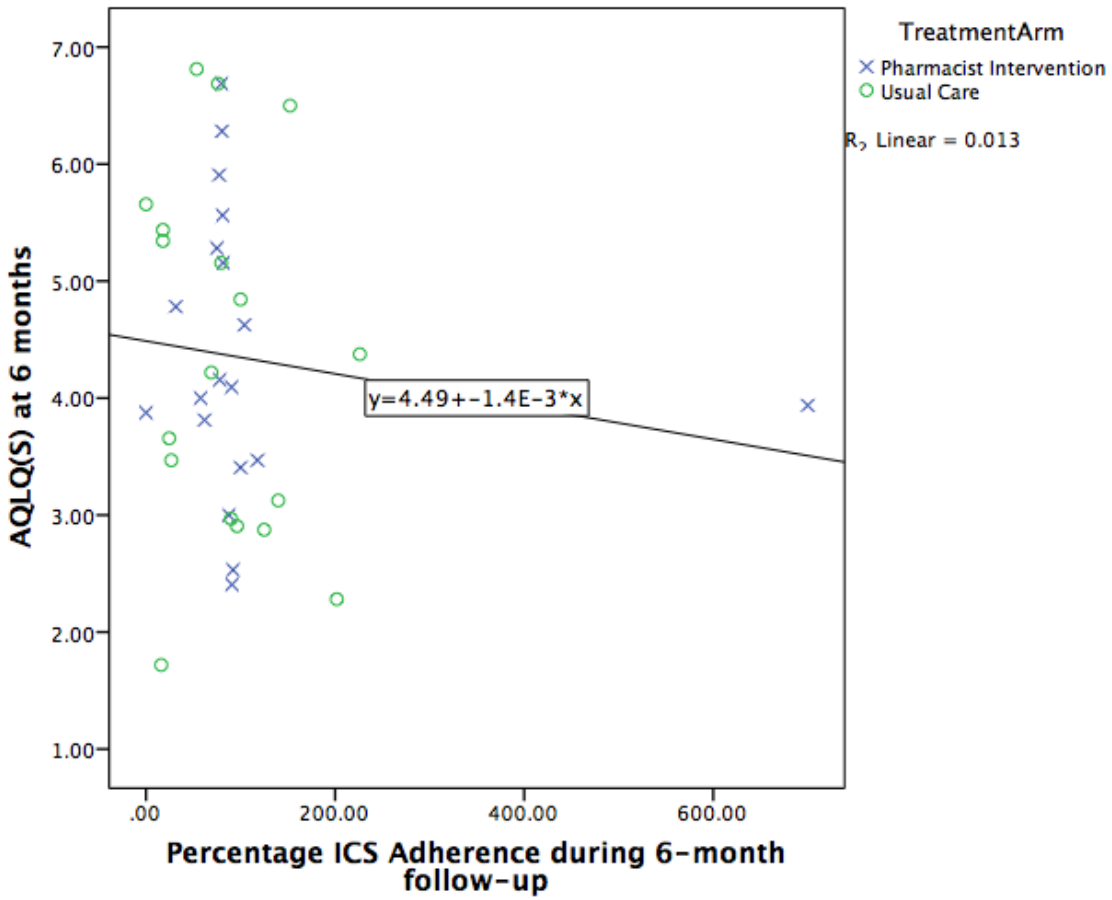


Figure 19. Scatter plot of adherence to ICS during the study and effect on asthma quality of life, measured using AQLQ(S) at the end of the study.

AQLQ(S), standardised asthma quality of life questionnaire; ICS, inhaled corticosteroid.

6 Discussion

6.1 Discussion of results

As outlined in the introduction, there is a lack of research investigating the role of pharmacists in managing the care of patients with difficult asthma, and this is the first study to investigate the effects of a redesigned pharmaceutical pathway across the primary and secondary care interface in patients with difficult asthma.

The results of this study demonstrates that the management of patients with difficult asthma through the provision of pharmaceutical care from hospital-based advanced clinical pharmacists is non-inferior to usual medical care in all asthma outcomes measured, including asthma control, quality of life, inhaler technique and overall adherence. Both the PI and UC groups were successful in stabilising asthma control and quality of life, with low rates of exacerbations and hospital admissions. Although overall adherence rates were similar in the PI and UC groups, there was a significantly greater increase in the proportion of patients in the PI group who had adherence rates 80-120% than in the UC group over the course of the study.

These outcomes were achieved despite most participants in the PI arm failing to receive the full protocol intervention, with only six of 26 participants having a t-MUR. Consequently few of the participants received any follow-up interventions as part of an MUR from community pharmacists to support and reinforce interventions performed during the initial baseline consultation performed by the hospital advanced clinical pharmacist. It is possible that study patients in both groups may have received additional interventions from their community pharmacist when collecting their dispensed prescription as part of routine practice. Data on this were not collected and so the extent to which this may have occurred is not known, nor whether this may have impacted on asthma control. However as MUR uptake was low, it is unlikely that a different service would have been provided to patients in the two groups and so the effects of any interventions performed would be unlikely to significantly affect the outcome measures in this study.

Potential explanations for the results of the study are discussed in this chapter, in order to understand how they may impact on clinical practice and to identify future areas for research.

6.1.1 Asthma control measures

The intention to treat results of the study demonstrate that the provision of pharmaceutical care from a hospital-based advanced clinical pharmacist was non-inferior to usual medical care for all asthma control measures including ACQ, exhaled nitric oxide, lung function, exacerbations and hospital admissions.

As expected for patients with difficult asthma attending the hospital clinic, all participants met the criteria for uncontrolled difficult asthma, having a median duration of instability of 3.5 years, a high median ACQ of 2.86 in the PI group and 3.00 in the UC group (where an ACQ score ≥1.0 on a 0-6 scale indicates uncontrolled asthma). This was despite treatment at Step 4 or 5 of the BTS/SIGN asthma guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014), and consequently patients required frequent OCS rescue courses (5.6 and 3.92 courses within the past 12 months respectively) and high use of SABA (49.0 and 45.5 puffs per week, respectively). Although participants randomised to the PI group had worse asthma control at baseline than those in the UC group, this difference was not statistically significant, and is unlikely to be clinically important. The study population was similar in all baseline characteristics to other difficult asthma populations reported in a UK multicentre registry of refractory asthma (Heaney et al., 2010), and so can be considered to be a representative sample, and thus the reported outcomes are relevant to UK practice.

There was no significant change in asthma outcome measures at 6-months compared to baseline levels, reflecting that asthma control did not deteriorate in either study arm over the course of the study. Participants in the PI group also achieved a significant reduction in corticosteroid rescue courses and SABA usage over a 3-month period immediately preceding consultations at follow-up compared to baseline, but this was not significantly different from participants in the UC group. Similarly the FE_{NO} level was not significantly different between

study groups at baseline or at 6-months, and so this study does not provide further data on the value of FE_{NO} for monitoring difficult asthma. However it remains uncertain why no difference in FE_{NO} values were observed, but may have been due to recruitment of patients with specific asthma phenotypes that are less responsive to ICS therapies, or may be due to a lack of effect on ICS adherence resulting in patients not taking effective doses of ICS.

Difficult asthma is a complex condition to manage because patients experience persistent symptoms and frequent exacerbations that may not be responsive to conventional asthma therapies, and there are many factors that may contribute to asthma-like symptoms (Barnes and Woolcock, 1998, British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Heaney et al., 2010). Consequently, the stabilisation of asthma control in both study groups, whilst reducing healthcare resource use in terms of rescue OCS courses and hospital admissions, can be regarded as a successful outcome (Sweeney et al., 2012, Heaney et al., 2010).

Most patients in the PI group only received interventions from the hospital-based advanced clinical pharmacist at the baseline consultation, as even for the six patients who received a t-MUR, very few new interventions were performed during these follow-up consultations. Therefore the majority of the impact from pharmacist interventions observed in this study may have been achieved only from the baseline consultation from the hospital-based advanced clinical pharmacist. This lack of follow-up interventions may have affected the asthma outcome results, although it is not clear whether these may have achieved additional benefit above the initial baseline consultation. The per protocol subgroup analysis of the six patients who received t-MUR failed to demonstrate any significant improvement in asthma outcomes compared to participants in the UC group, but this is likely to be because there were insufficient participants to ensure that this subgroup analysis was adequately powered to demonstrate any significant change in ACQ. Consequently although the current study adds new evidence on the effects of pharmaceutical care provided by a hospital specialist pharmacist it did not determine the effects of combined pharmaceutical care provided by primary and secondary care pharmacists. However the study does provide valuable learning about the challenges of

‘joining up’ pharmaceutical care, which can support the development of future study designs.

The results of this study mirror those reported in the BREATHE study, which was a community pharmacy based interventional study that recruited a similar uncontrolled asthma patient population to the present study (Charrois et al., 2006). In the BREATHE study, there was no detectable difference in asthma outcomes between the intervention and usual care group, despite being adequately powered to detect a significant difference in ACQ score between the two groups (Charrois et al., 2004). The authors believed this lack of demonstrated effect was due to an imbalance between the study groups, contamination of usual care and poor implementation of the intervention. The present study differs from the BREATHE study in that participants in the two arms were well balanced at baseline and more interventions were performed in the PI than in the UC group. Participants in the PI group received individualised interventions addressing their medication, inhaler technique, educational needs, associated medical conditions depending on their identified needs, whilst seven in the UC group received no intervention at all. A possible criticism of the interventions performed at baseline is that there was no consistency in the type of interventions performed for all participants, and so it is not possible to determine whether any specific intervention may result in more favourable outcomes. For example, retrospective data from this study suggests that the provision of asthma action plans and interventions seeking to improve adherence should have been performed more consistently, because not all patients received an action plan and poor adherence appears common place.

In contrast, the findings of this study differ from complex interventional studies in community pharmacy settings, which have demonstrated statistically significant improvements in asthma severity based on the Australian National Asthma Council asthma severity assessment table, although these studies recruited a more mixed population of asthma severity (Armour et al., 2007, Saini et al., 2008). Both of these studies compared enhanced pharmaceutical care to usual pharmaceutical care and supported the initial intervention with repeated follow-up consultations. Participants were recruited to these studies if medical care was difficult to access, which may explain the poor response in the usual

care arm. In addition, a certain degree of caution is necessary when comparing to this study as the criteria used to define asthma severity were different and the study populations included patients with both mild and severe asthma. Furthermore, both studies were successful in ensuring that all patients received regular follow-up to reinforce the educational interventions provided to patients, which may have contributed to the positive outcomes that were demonstrated.

In these studies, 85% (Saini et al., 2008) and 94% (Armour et al., 2007) of patients who completed the study attended the first follow-up visit, four-weeks after the initial consultation, allowing pharmacists to reinforce the education interventions from the baseline consultation, and this may have contributed to the positive outcomes reported. In one study, the authors commented that this high retention rate might be due to patients valuing the service provided by their pharmacist at the baseline consultation, which persuaded them to return (Saini et al., 2008). In the present study, patients were aware that the follow-up consultations were to be provided by a different pharmacist outside of the specialist difficult asthma clinic, and this might have contributed to the poor uptake of the t-MUR service, whether or not they valued the service provided by the hospital advanced clinical pharmacist. However as no service evaluation data were collected, it is not possible to determine actual patient's opinions of the value of consultations provided by the pharmacists in either the difficult asthma clinic, nor in community pharmacies.

Comparing the results of the present study with other studies is difficult due to variations in the interventions performed and asthma outcomes reported. However, when comparing to the above three studies (Armour et al., 2007, Charrois et al., 2006, Saini et al., 2008), a number of implications for routine practice are highlighted. Firstly, interventions such as assessing adherence and providing asthma action plans should be performed more consistently, and secondly, initial baseline interventions should be supported with follow-up consultations.

6.1.2 Quality of life

The intention to treat results of the study demonstrate that the provision of pharmaceutical care from a hospital-based advanced clinical pharmacist was

non inferior to usual medical care for both quality of life measures used, with quality of life remaining stable in both groups throughout the six-month study.

Participants in both study groups in this study were moderately to very limited in their asthma quality of life as demonstrated by mid-range scores in the AQLQ(S), and this was consistent across all four domains in the questionnaire (symptoms, activity limitation, emotional function and environmental stimuli). Similarly at least half of the participants in both groups reported general problems on the EQ-5D-5L with mobility, usual activities, anxiety or depression and pain or discomfort – all conceivably, but not necessarily, due to asthma. This establishes that participants had a poor quality of life at baseline and follow-up, which is unsurprising considering that long-term persistent asthma symptoms and frequent exacerbations place people with difficult asthma under a very substantial burden, which is known to adversely affect health related quality of life measures (Lloyd et al., 2007). It has previously been shown that poor or worsening asthma control and exacerbations can affect day-to-day life and worsen quality of life (Juniper et al., 1999a, Lloyd et al., 2007). This may explain why both study groups were successful in preventing quality of life measures deteriorating, as asthma control was stabilised in both groups and few patients experienced any exacerbations.

Previous studies have similarly failed to demonstrate any discernible changes in either asthma-related quality of life or general health status following complex pharmacy interventions, although this could be due to the inclusion of patients with well controlled asthma (Mehuys et al., 2008) or use of un-validated measures of quality of life (Petkova, 2008). However some pharmacist interventional studies have demonstrated improvements in asthma-related quality of life (Armour et al., 2007, Kritikos et al., 2007, Cordina et al., 2001), and whilst two of these studies included repeated follow-up to reinforce the interventions, which may have helped achieve significant improvements in quality of life (Armour et al., 2007, Cordina et al., 2001), the third was of short duration only, and did not measure long-term improvements in asthma outcomes (Kritikos et al., 2007).

Consequently, to achieve a significant improvement in quality of life in people with uncontrolled asthma, repeated reinforcement of interventions such as asthma education, inhaler technique training and adherence counselling may be a necessity.

6.1.3 Inhaler technique

The study protocol recognised that inhaler technique was of key importance in the study because there is increasing evidence demonstrating that uncontrolled asthma is associated with poor inhaler technique (Baddar et al., 2014, Giraud et al., 2011, Giraud and Roche, 2002, Melani et al., 2011), and may be particularly so where patients perform critical errors (Basheti et al., 2014, Melani et al., 2011, Molimard et al., 2003). Despite this, inhaler technique training by pharmacists as part of routine practice in the current study was found to be poor, with only five who had previously received inhaler technique training from a community pharmacist and only four from a hospital pharmacist. Furthermore, fewer than half had received training from their practice nurse or GP, which is likely to account for the poor inhaler technique observed in both the PI and UC group at baseline.

The results of the baseline intervention demonstrate significant improvements in inhaler technique measured using inhaler technique score for pMDI, Accuhaler and Turbohaler devices in the PI group, but only the pMDI device in the UC group. This confirms the findings of previous studies that have reported the benefits of using In Check DIAL inspiratory flow meters to improve IFR (Alamoudi, 2003), and pharmacists' ability to correct inhaler technique (Basheti et al., 2008, Basheti et al., 2005). Despite initial improvements in inhaler technique at baseline in the present study, the proportion of participants with optimal inhaler technique was significantly lower at 6 months, indicating that the benefit of the baseline intervention dissipated over time. In the PI group, this was likely to have resulted from a lack of reinforcement of correct inhaler technique and follow-up interventions because most participants did not receive a t-MUR. Since maintaining correct inhaler technique over long periods of time has been shown to improve asthma outcomes through the use of regular and repeated education (Basheti et al., 2008), lack of the follow-up t-MUR is likely to have been an important factor in the failure to demonstrate significant effects on

asthma outcomes at 6-months in this study. However in the present study, a deterioration in inhaler technique was also observed in the six patients who received a t-MUR at a mean 60 days (range 28 – 143 days) following the baseline consultation, which suggests that inhaler technique training should be repeated sooner than two months after initial training. It is also likely that inhaler technique should be repeated regularly after t-MURs. An alternative explanation for the deterioration in inhaler technique may be that the education method was not effective to achieve long-term improvements. One similar previous study that assessed inhaler technique training used a similar method that included checklists, verbal and physical demonstration to train patients, and achieved and maintained improvements in inhaler technique over 6 months (Basheti et al., 2008). In contrast to the present study, reinforcement training was provided at one, two and three months, and all patients were provided with sticky labels attached to their inhaler devices to outline correct inhaler technique. Consequently, these sticky labels may be critical to maintaining correct inhaler technique, although further studies would be required to confirm this.

Ensuring optimal inhaler technique is recommended in the management of respiratory conditions such as asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014), but is complicated by the diversity of inhaler device currently available in the UK market. This is highlighted by the fact that the 52 participants used eight different types of inhaler devices, and participants were often prescribed two or three different devices at the same time.

The need to use different devices may create an additional burden for patients because of the need not only to remember several different types of action but also to correctly apply them to the appropriate device. Consequently some guidelines recommend that the same inhaler device should be prescribed when more than one inhaled drug is required (Dolovich et al., 2005), as this would make inhaler technique training quicker and easier because patients would only need to learn one technique. However this is not always possible as the some devices are only available in a limited range of drugs, and consequently two or more inhaler devices are commonly required.

It has been well established that knowledge of correct inhaler technique amongst healthcare professionals is poor (Baddar et al., 2001, Baverstock et al., 2010, Interiano and Guntupalli, 1993, Jackevicius and Chapman, 1999, Jones et al., 1995), and the wide variety of inhaler devices available for asthma treatment is likely to make it harder for healthcare professionals to achieve competence with all devices. It is unsurprising that inhaler technique was poor at baseline despite all patients receiving training in the past, specifically participants frequently had an IFR that was too fast for low resistance aerosol inhalers such as the pDMI and Easi-Breathe devices, and consequently the majority of pMDI users in particular had unsatisfactory inhaler technique. It is disappointing that poor inhaler technique continues to be reported as a major problem in this and other studies (see **Chapter 2.2.2**), despite being critical to asthma treatment. The poor inhaler technique at baseline may be a consequence of poor training from healthcare professionals who may be unfamiliar with these devices, or due to participants forgetting the correct technique since they were last instructed. This suggests that regularly repeated education is necessary for both patients and healthcare professionals; to ensure that inhaler devices are used correctly in order to achieve the maximum clinical effect from inhaled drugs and improve asthma outcomes.

Analysis of the number of interventions made during baseline consultations demonstrate that pharmacists were significantly more likely to document interventions addressing inhaler technique (24 vs. 4) than physicians providing usual care, suggesting that pharmacists may be better at assessing and/or identifying poor inhaler technique. However since there was no independent evaluation of the quality of the inhaler technique assessments performed in either study group, it is not possible to confirm this assertion.

6.1.3.1 Evaluation of inhaler technique assessments

6.1.3.1.1 Inhaler technique checklists

This study was designed as a real-life interventional study, and as such there was no restriction on the medicines used to treat each participant's asthma. As a consequence, there was a wide range of inhaler devices used by patients and the majority of patients used at least two different types of inhaler device. This introduces a further limitation into the study, since it makes it difficult to compare

ability to use inhalers between different inhaler devices because each requires a different technique to load and prime, inhale through and close after using. This is evident by having separate checklists for each device (**Appendix 8**), with different total numbers of steps and a different number of potential critical errors per device (Haughney et al., 2010). As a consequence, inhaler technique score had to be standardised by calculating the percentage of correct steps performed, but should be interpreted with caution as some inhaler devices are easier to use and less complicated than others (Lenney et al., 2000).

Although a checklist was used to determine each participants inhaler technique there are a number of issues that should be considered when using these, primarily that there is no standard checklist available, with one review identifying 24 checklists for Accuhaler devices and 16 for Turbohalers (Basheti et al., 2014), with substantial variation. This makes comparison between different studies difficult, even though the checklist used in this study is almost identical to those recommended in the review article (Basheti et al., 2014), which increases the confidence that the checklists used were valid. Differences in the present study compared to recommended checklists (Basheti et al., 2014) include having a step to ensure that the Turbohaler cap is replaced after use, and that exhaling away from the inhaler mouthpiece before use was classed as a critical step because exhalation through the mouthpiece can blow dry powder away.

6.1.3.1.2 Inhaler technique assessment

Inhaler technique score is commonly used in studies, but does not necessarily indicate how much of the dose each participant would receive because one error would still give a high score, but if it was a critical error the patient could potentially receive none of the dose. Consequently a greater emphasis on critical errors in inhaler technique is becoming more recognised (Molimard et al., 2003, Basheti et al., 2008, Basheti et al., 2014, Basheti et al., 2011, Basheti et al., 2005, Haughney et al., 2010). As participants used a wide variety of inhaler devices, a pragmatic decision was made to perform statistical analyses by assuming that inhaler technique scores were equivalent for all devices, despite the limitations of this. A second analysis was performed to report the proportion of patients with optimal technique (all steps in the checklist

performed correctly) and the proportion with satisfactory technique (all critical steps identified in each checklist correct), since the latter measures may be more likely to identify the proportion of patients likely to receive an effective dose and may therefore impact on clinical outcomes (Basheti et al., 2014).

Even this approach will still have some limitations due to the variety of inhaler devices used by the study participants and this may have affected the data analysis. An alternative study methodology would have been to only recruit patients using one specified inhaler device since inhaler technique scores and the proportion with optimal and satisfactory inhaler technique could more precisely be studied. However, this would have restricted the potential number of patients in the difficult asthma clinic who could be suitable for this study, and may not have allowed an adequate study sample size to be recruited within the study timeframes. Furthermore, this would not have reflected usual clinical practice because there is no one inhaler device that is appropriate for every patient, and so would have prevented a real-life pragmatic study being performed.

Whilst there was no significant difference in the proportion of participants with optimal inhaler technique at baseline and follow-up, it should be noted that this study was not adequately powered to determine this outcome, since there were not enough participants using each inhaler device to provide an adequate sample size for these analyses. This is demonstrated using a sample size calculation for comparison of proportions:

$$n = (Z_\alpha + Z_{2\beta})^2 \{\pi_1(1 - \pi_1) + \pi_2(1 - \pi_2)\} / \delta^2$$

Where:

n =	The approximate number of patients per group
π_1 =	The proportion of participants in the UC group with optimal inhaler technique
π_2 =	The proportion of participants in the PI group with optimal inhaler technique
δ =	The difference in proportions between the PI and UC groups
$(Z_\alpha + Z_{2\beta})^2$ =	A function based on Study Power of 80% (=7.849)

Consequently, based on the study results where optimal technique at follow-up was observed in 6.1% and 7.3% of participants using pMDI, 75% and 61% using Accuhalers and 71.4% and 42.9% using Turbohalers, the total number of patients required in a study would be 30,658, 299 and 87 respectively. However, if the as per protocol intervention had been completed with all PI participants receiving t-MURs, it is possible that more patients would have had optimal inhaler technique at follow-up in the PI group, as other studies have demonstrated that improved inhaler technique for prolonged periods can be achieved with regular follow-up (Basheti et al., 2008). Consequently the required sample size is likely to have been smaller than this estimate, as the difference in proportion of patients achieving optimal inhaler technique may be greater with repeated follow-up than with the one-off intervention provided to patients in the current study.

The overall results on inhaler technique have major implications for practice, as they demonstrate the vital importance of ensuring that every patient with asthma has their inhaler technique checked and corrected more frequently than current practice, in order to maintain optimal inhaler technique. It is possible that this should be done at every contact with healthcare professionals, whether during primary or secondary care consultations and when collecting prescriptions from community pharmacies. It should never be assumed that inhaler technique has been checked before, or by someone else, nor can it be expected to be as good as it was when previously checked.

6.1.4 Inhaler preference

A frequently overlooked issue in the management of asthma concerns patients' preference for different inhaler devices, as this may affect adherence (Capstick and Clifton, 2012, Dolovich et al., 2005). However there are few published independent patient preference studies, and a review of evidence found that the majority of studies are sponsored by the pharmaceutical industry and the majority also report that patients prefer the device manufactured by the sponsoring company (Anderson, 2005). Assessment of both patient preference and linkage to data on adherence (prescriptions issued) were therefore included in the study design. Two different methods were used to assess patient preference of seven different inhaler devices in this study, Both scoring systems

were consistent in the resulting rankings, showing that the Easi-Breathe device was most preferred, confirming findings from previous independent studies (Lenney et al., 2000), and indicating that the results from the current study may be generalisable to the overall asthma population.

These results suggest that prescribing inhaled drugs in an Easi-Breathe device would be well accepted by most patients probably due to the ease and simplicity of use of this device, and may consequently improve adherence. However the Easi-Breathe device is only available for two drugs: beclometasone (Qvar®) and salbutamol, of which beclometasone without a LABA is only appropriate for treating patients with mild asthma at step 2 of the BTS/SIGN asthma guidelines (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). The Easi-Breathe inhaler is therefore not suitable for participants in a difficult asthma study, and consequently alternative inhaler devices are required.

As the Easi-Breathe inhaler was found to be the preferred device in this and a previous study (Lenney et al., 2000), this suggests that there is a need for other classes of drug in this device. Alternatively, manufacturers should develop other inhaler devices that have a similarly easy method for use: open cap, inhale, close cap. Since this study commenced, a number of novel inhaler devices have been launched in the UK, including the Ellipta® (GlaxoSmithKline), Spiromax® (Teva) and NEXThaler® (Chiesi), with a similar three-step method for use to the Easi-Breathe device. Each of these three new devices are available as ICS/LABA combinations for the treatment of asthma, and may be easier to use than other existing inhaler devices (Svedsater et al., 2013, Voshaar et al., 2013). Consequently the data from this preference analysis may already be out of date in the context of the increasing range of inhaler devices available to patients.

Alternative devices that were well liked (rank 2 to 4) by patients, and potentially suitable for most patients with difficult asthma were Turbohaler, pMDI and Accuhaler using both ranking systems.

Whilst the least preferred inhaler devices in this study were the Easyhaler, HandiHaler and Respimat devices, it should be recognised that these devices were not commonly prescribed. Prior to the study, no patients in the PI group were prescribed an Easyhaler or Respimat, and four were prescribed a HandiHaler. In contrast more than half of the patients were prescribed a pMDI (19) or Turbohaler (17), and 10 were prescribed an Accuhaler. One recent patient preference study was reported that previous experiences with inhaler devices impacts on individual patients' rankings even when asked to rate them only based on physical and functional aspects of the devices (Chorão et al., 2014). Although not assessed in the current study, the results of the preference analysis may also have been influenced by current and previous use of inhaler devices, despite the fact that no patients had previously used the top ranking Easi-Breathe device.

There are important implications for practice from preference analyses because there may be contrasting opinions between patients and healthcare professional's about which device is most appropriate, when views on patient's preference are balanced with their ability to use an inhaler device. Although there appeared to be no link between patient preference and inhaler technique guiding prescribing decisions on asthma outcomes, it is important that patient preference and inhaler technique assessments are considered equally during a concordant consultation in order to agree the best and most appropriate device to be used.

6.1.5 Adherence

The baseline consultations were clearly not effective or accurate methods to identify non-adherence as only 6 and 4 participants in the PI and UC groups were identified as needing adherence counselling, compared to retrospective prescription data, which demonstrated that the majority of participants in both groups were non-adherent. This is unsurprising as asthma patients are known to overestimate their true adherence (Axelsson et al., 2009).

Prescription data in this study found that 57.5% of participants had adherence rates less than 80%, 35% had adherence rates less than 50% and 17.5% had adherence rates exceeding 100% over the previous six months. This is

consistent with previous research on adherence in asthma; one systematic review found that 24-69% of asthma patients underused and 30-60% overused their ICS (Cochrane et al., 2000), whilst in difficult asthma populations, one study reported that 35% collect fewer than half their ICS prescriptions and 21% filled more than 100% of their prescriptions (Gamble et al., 2009).

This study found that the increase in proportion of patients with adherence rates 80-120% was significantly greater in the PI than the UC group over the course of the study, and demonstrates that pharmacist care had a greater impact on adherence than physicians. This study was adequately powered to detect this effect, since using the sample size calculation for comparison of proportions on **Page 170,** a sample size of 15 patients per group is required for this analysis. However the precise reasons for improved adherence in the PI group are a matter for conjecture as they were not studied, but could be due to improvements in inhaler technique achieving greater symptomatic benefits reinforcing adherence through greater perceived benefit, or education of the role of medication reinforcing adherence. Classification of adherence in the range 80-120% is justified as it has been used in previous pharmacist intervention studies (Armour et al., 2007), which also demonstrated improvements in adherence in PI patients.

Prescription records are considered a more accurate measure of adherence, than patient self-report, but caution is still advised as prescription data cannot show whether the patient collected their prescription from the pharmacy or whether they actually used their inhalers (Cochrane et al., 1999, Osterberg and Blaschke, 2005), and will not take in to account whether patients have previously received an oversupply, so non-collection of a prescription may be appropriate. This study tried to make the use of prescription data more robust by identifying all issues from each patients GP and hospital Trust over a six-month period, as a longer duration of data could reduce the impact of inaccuracies in adherence rate calculations caused by one-off mitigating factors such as excess stock. However, the method used to collect prescription data could still have missed some issues, such as any that may have been received from hospitals outside the local area, although since hospital admissions were low, it is unlikely to have significantly affected the overall adherence data.

The MARS was used as a corroborating measure of adherence in this study, and it is interesting to note that the MARS questionnaire was more successful in identifying non-adherence than patient self-reporting during consultations, but still underestimated adherence compared to measurements using prescription data. The MARS may be more accurate than asking patients about adherence during consultations, because patients may be afraid of admitting to their physician about not taking their medicines, feeling less threatened by a questionnaire, or due to the non-confrontational questions used in the MARs (Haughney et al., 2008).

The MARS has been validated in a number of studies (Horne and Weinman, 2002) and has been shown to correlate well with other measures of adherence such as pharmacy prescribing records (Menckeberg et al., 2008). This study provides further data that the MARS questionnaire is a useful tool to determine adherence, and also provides useful insight into how patients use their inhalers, as significant proportions of participants in this study admitted to altering their ICS dose, taking more than instructed, or even stopping their ICS for periods of time. Over the course of the 6-month study, the only non-adherent behaviour that was found to have significantly changed was the proportion of participants in the PI group that admitted to stopping their ICS for periods of time. This contrasts with prescription records for adherence, which suggested that participants in the PI group were more adherent at 6-months than at baseline. Consequently it is likely that both prescription records and MARs data should be interpreted with caution in the absence of clear objective adherence assessments.

The BMQ (Horne et al., 1999) is recommended as a useful tool to facilitate optimal adherence (Haughney et al., 2008), as it can be used to identify potential perceptual and practical barriers to adherence in individual patients with asthma because it assesses each patient’s beliefs about the need for regular preventer therapy for controlling their asthma, and their concerns about potential adverse effects of treatment.

This study found that patients rated that they had a general awareness of the necessity to take their medicines to manage their asthma using the BMQ. However on average, participants in both groups neither agreed nor disagreed about whether they had concerns about having to take medicines or their potential harm, nor whether healthcare professionals overuse them. These data contrast with previous research that has found that patients with controlled and uncontrolled asthma have a number of concerns about their medicines, with many having doubts about the necessity for their medicines, have concerns over the side effects and consequences of medicines, and perceptions over their illness (Axelsson et al., 2009, Bolman et al., 2011, Clark et al., 2012, Horne and Weinman, 1999, Horne and Weinman, 2002, Menckeberg et al., 2008, Park et al., 2010, Sofianou et al., 2013). This suggests that participants recruited to this study may have been more informed about their medication that participants in other studies, or that the perceived need for medicines to treat their difficult asthma outweighed any concerns they may have had. Consequently the BMQ data should infer that the study population would have had good adherence, which was not the case when prescription data was used to quantify actual adherence.

Whilst this study found that poor adherence was widespread, it did not confirm an association with asthma control. However due to the study design and practicalities over recruitment to the study, it was not possible to collect prescription data on adherence in time for the first consultation, as many GP practices took up to two weeks to provide the data and would provide it only with patient consent. Therefore during the baseline consultation, an assumption had to be made that patients were adherent to treatment if they stated they were during consultations. In addition the BMQ and MARS questionnaire responses were not reviewed in either the PI or UC group due to concerns that interpreting both questionnaires would unduly prolong each participants attendance in the clinic. Furthermore, there were concerns that if participants knew their answers were going to be read prior to the consultation, they would modify their answers and feel compelled to report good adherence.

The data on adherence in the difficult asthma population in this study suggests that a greater emphasis should be placed on adherence in difficult asthma. GPs

or primary care pharmacists should review prescription records to determine adherence rates in patients with uncontrolled asthma prior to referral to secondary care clinics. In addition, when GPs refer patients to difficult asthma clinics for specialist review and assessment, they should be asked to provide prescription data to enable an adherence assessment to be performed. Alternatively, a patient record that is shared across primary and secondary care sectors could allow all healthcare professionals to review adherence data when needed. In addition, the MARS questionnaire also appears to be a useful tool to identify non-adherence and should be used routinely, whilst the BMQ did not appear to add value in this patient group.

It is interesting that bivariate correlation found no significant relationship between adherence to ICS treatment and either asthma control or asthma quality of life, as it was anticipated that patients who used their ICS inhalers on a regular basis would have more effectively treated asthma and improved asthma outcomes. The failure to find such an association again suggests that prescription data may not be an accurate reflection of true adherence, or that other unidentified factors have significant effects on asthma control.

6.1.6 Asthma reviews and complex interventions

Asthma reviews were performed in the PI group using consultation styles based on those discussed in the methodology (see **Chapter 4.5**). This was important because the nature of the study required the pharmacist, who performed the baseline interventions to participants in the PI group to develop a collaborative partnership in order to encourage participants to discuss their asthma symptoms, triggers and treatments (Kurtz et al., 2003). The collaborative partnership approach would then allow the pharmacist and patient to discuss the advantages and disadvantages of different treatment options and how they may affect the lifestyle and asthma control, which allowed different interventions to be agreed. No data were collected on the consultation style used in the UC group.

This study did not seek to investigate the opinions of participants about how their asthma consultations were performed in either study group. However participants in the PI group generally appeared to value them, as some

provided positive feedback at the end of the consultation about receiving new information about their asthma and treatments. In contrast, one patient in the PI group was less positive about the consultation, explaining that it was too long as a consequence of completing so many questionnaires and due to the number of interventions required. On reflection, patient evaluation of the baseline consultations would have been a valuable method to assess consultation style and performance as the pharmacist researcher, which would have allowed me to understand how I could improve my practice, or to determine how the consultation style may have affected the study outcomes (Bowling, 2002).

This study was designed as a complex interventional study on the basis that previous studies have demonstrated that single interventional studies in asthma are not as effective as complex interventions (Gibson et al., 2002a, Gibson et al., 2002b). As this was a pharmacist interventional study, the interventions considered appropriate in this study were typically related to medication, in particular inhaler technique, education, and provision of asthma action plans. These are all well recognised to be effective in asthma management (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Global Initiative for Asthma, 2014), and are similar to those used successfully in other pharmacist complex interventional studies (Armour et al., 2007, Barbanel et al., 2003, Charrois et al., 2006, Cordina et al., 2001, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Mehuys et al., 2008, Petkova, 2008, Saini et al., 2008).

Since pharmacists are recognised as medicines experts, it is not surprising that there were significantly more medicines-related interventions performed in this study in the PI rather than the UC group. The fact that so many interventions were identified and performed compared to the UC group, suggests that pharmacists have a different skill set to physicians and are able to identify otherwise unidentified medicines-related issues where there are opportunities to improving asthma management.

A potential drawback with performing so many interventions during initial consultations is that the increasing number and complexity could cause confusion or provide too much information that patients may then struggle to

retain. It was for this reason that follow-up reinforcement interventions through t-MURs were included in this study design. This was thought particularly important since previous studies have demonstrated that patients who received interventions focusing on improving inhaler technique began to lose their skills towards the end of a six-month study even with repeated follow-up (Basheti et al., 2008). It is uncertain whether patients with difficult asthma would benefit more from receiving fewer interventions at each consultation, or from receiving greater number of interventions supported by regular and repeated reinforcement from community pharmacists. Future research should be directed to examining the role of follow-up support and management from community pharmacists to determine the optimum or practicable and cost-effective number and frequency of consultations to improve and maintain asthma control in such complex cases.

Analysis of the interventions performed suggests that there were certain interventions that were poorly performed in both the PI and UC groups. Asthma action plans were only provided to 11.5% and 23.1% of participants in the PI and UC groups respectively, despite less than two thirds having action plans at baseline. The rationale for not providing action plans was not collected, although there may have been legitimate reasons for this. For example, some patients in the current study were not thought able to monitor their asthma and use an action plan appropriately to adjust their medication and so were advised to stick to the same regular dose at all times, whilst other studies have reported that not all patients will take ownership of their asthma management and use an Action Plan (Armour et al., 2007).

6.1.7 The role of MURs to provide follow-up consultations

Regular follow-up has been incorporated into most other pharmacist complex intervention studies in asthma because the impact of interventions could similarly decline over time (Armour et al., 2007, Barbanel et al., 2003, Basheti et al., 2008, Charrois et al., 2006, Cordina et al., 2001, Garcia-Cardenas et al., 2013, Kritikos et al., 2007, Mehuys et al., 2008, Petkova, 2008, Saini et al., 2008). This follow-up may be of importance as previous pharmacist interventional studies have demonstrated that improvements in inhaler technique following education and training may begin to decline during long

follow-up periods (Basheti et al., 2008). In the present study, the initial improvement in inhaler technique was not maintained over the course of the study, which highlights the potential importance that follow-up consultations may have in reinforcing education provided during initial consultations.

To allow for follow-up consultations for participants in the PI group, community pharmacists were identified as being well placed to perform t-MURs, reinforce baseline interventions, and to perform any new interventions identified as necessary. Previous studies have demonstrated that asthma MURs are well accepted by patients and effective in improving asthma control (Bagole et al., 2007, Portlock et al., 2009, MacAdam and Sherwood, 2011, The Cambridge Consortium, 2012), so there was a high degree of confidence that they would be utilised by patients in this study.

It was disappointing that a major limitation of this study was that very few participants in the PI group actually received a t-MUR, despite each participant's community pharmacist being contacted verbally and in writing by the lead researcher. Furthermore, this study had been publicised during a series of educational sessions on asthma and inhaler technique preceding the study, as well as in a newsletter from the Leeds, Bradford & Airedale, Calderdale & Kirklees Local Pharmaceutical Committees (now Community Pharmacy West Yorkshire). This failure to provide follow-up interventions and reinforce education and advice may have contributed to inhaler technique being significantly worse at 6-months compared to baseline and also the failure to demonstrate improvements in asthma outcomes. It was concerning that the most common reason reported by community pharmacists for not performing a t-MUR was the patient's failure to attend, whilst the most common reason given by participants was that the community pharmacist did not arrange one. This suggests that there was either a communication mismatch between community pharmacists and patients, or perhaps that the explanations provided were not always truthful. It was also concerning that one pharmacist did not perform a t-MUR because they did not feel confident that performing a t-MUR would provide any benefit to the patient compared to healthcare professionals working in a difficult asthma clinic. Since the rationale for the t-MUR was to reinforce interventions already performed, check and optimise inhaler technique and

perform a standard MUR, every community pharmacist should be competent to perform this role. This suggests that some pharmacists do not yet understand the valuable contribution to asthma control that their MUR could make, despite other studies reporting that pharmacists have noticed a positive impact on health after performing MURs with patients (Waterfield and Dhir, 2011).

A potential reason for the poor completion rates of t-MURs could be the relatively limited communication between secondary and primary care, although brief, written referrals for t-MURs were provided for all patients. This theory is supported by a systematic review that reported that poor communication and information transfer to primary care at discharge following hospital admissions was frequent and thought to adversely affect patient care (Kripalani et al., 2007), whilst lack of access to medical notes has been raised as a concern over MUR provision by GPs (Celino et al., 2007). It is conceivable that community pharmacists may have had similar concerns in this study and whilst there were no reports of problems with the referral forms, a greater uptake of t-MURs may have been achieved by providing each community pharmacist with a copy of the clinic letter from the initial baseline consultation in the difficult asthma clinic. Consideration should also be made to making patient medical records available to community pharmacists providing advanced pharmacy services such as MURs, as well as rolling out access to summary care records to community pharmacists that is planned from October 2014 as a proof of concept project (Health and Social Care Information Centre, 2014).

Potential strategies to improve the uptake of t-MURs could have included telephone reminders to participants and community pharmacists, and even personal visits from the lead researcher to review the study protocol prior to the t-MUR being performed and provide any ad hoc education felt necessary by either the researcher or the community pharmacist. However this was not feasible within a research study that was funded to provide one day per week of research time.

An alternative strategy to ensure follow-up interventions in the PI group would have been to ask each participant to attend the difficult asthma clinic at regular intervals following the baseline consultation. However, although this was initially

considered, it was ruled out because it was thought that providing additional intervention consultations closer to the patient's home in their community pharmacy would be more likely to achieve good attendance than asking patients to re-attend the hospital outpatient clinic. Secondly, the difficult asthma clinic had limited capacity to allow extra visits and is also not funded by local Clinical Commissioning Groups to provide additional follow-up visits compared to routine practice. Similarly, research funding did not request funding to allow hospital follow-up interventions as the funding submission was requested anticipating that participants would receive t-MURs.

6.2 Critical appraisal of this study

6.2.1 Aims and objectives

This study aimed to examine the effects of a co-ordinated management strategy between primary and secondary care pharmacists on asthma control and quality of life in patients with difficult asthma. The primary objective was to measure asthma control using ACQ, and secondary objectives measuring other important outcomes including quality of life, exacerbations, lung function, inhaler technique and adherence. Whilst the study design was largely successful in collecting these data at baseline and at six months follow-up, there were a number of strengths and limitations in the study that will now be discussed.

6.2.2 Literature review

As discussed in **Chapter 3.2**, the literature review used to inform the study design was based on methods recommended by the Cochrane Collaboration for performing systematic reviews (Higgins and Green, 2011). This review was done independently since it formed the basis of a research study performed under supervision for award of Doctor of Pharmacy programme. However Cochrane advise that literature searches should be undertaken by a person who has expertise in designing search strategies for use in bibliographic databases in order to identify all relevant published articles (Higgins and Green, 2011). This person may be a trials search co-ordinator, a local healthcare librarian or information specialist. Similarly, two reviewers are recommended to

ensure that articles included for the literature review meet the inclusion criteria and that those that don't are excluded (Higgins and Green, 2011).

The implications of the independent approach to performing the literature review should be considered, since there is a risk that suitable studies for inclusion in the review were not identified, particularly as the search strategies used identified a large number of articles. A weakness of the search strategy is that a 'Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE' was not incorporated into the search strategies, as this would have reduced the number of identified articles to more manageable levels (Higgins and Green, 2011), and reduce the risk of accidentally overlooking relevant articles.

On reflection, it would have been prudent to review planned search strategies with someone with expertise in designing search strategies to ensure that it was focused and ensure that relevant articles were not missed. The search strategies were discussed retrospectively with a colleague who is a medicines information specialist, who considered the search strategy to be adequate to meet the requirements of the set inclusion criteria, although it could have been focused to a greater extent to prevent it yielding large numbers of irrelevant articles.

6.2.3 Study design

6.2.3.1 Methodology

As the study was designed as a pragmatic (real-life) complex intervention in a real-life setting, a prospective un-blinded randomised study design was chosen, as described in **Chapter 4.2**. A prospective study was required, since it would have been impossible to collect data retrospectively, because the majority of outcomes being tested were not routinely recorded in the difficult asthma clinic, including objective inhaler technique assessment or asthma outcome measures such as Juniper's ACQ and AQLQ(S). The lack of missing data for these outcome measures justifies that the prospective study design was appropriate.

The study setting in a hospital difficult asthma clinic could be noted as a factor that contributed to the low uptake of t-MURs by participants in the PI group,

because this required them to receive follow-up consultations from a different pharmacist at a separate location. A previous study reported that patients may return for follow-up consultations provided by pharmacists after having a positive experience during the first visit (Saini et al., 2008). In the current study, it was not possible to provide follow-up visits at the same hospital difficult-asthma clinic, and so patients were referred to their usual community pharmacist for a t-MUR. Whilst they may have a good relationship with their regular pharmacist when collecting their prescription, this does not necessarily indicate trust to manage a complex condition such as difficult asthma when a specialist consultant physician usually manages them. Although none of the patients in the study reported lack of trust in their community pharmacist, this as well as other reported reasons for poor uptake of t-MURs such as communication difficulties, should be considered for future research studies investigating joined up care between primary and secondary care pharmacists.

As there were risks associated with the role of the lead investigator as an insider researcher, it was important to mitigate against the potential for bias being introduced into the study. This was complicated by the fact that funding was not available to allow for independent data collection and analysis and so there is a potential for performance and detection bias to have inadvertently being introduced into the study (Higgins and Green, 2011). In order to reduce this risk of this occurring, the study design incorporated as many objective and/or patient-completed outcome measures as possible. Such measures included the primary outcome measure ACQ, as well as secondary outcome measures including AQLQ(S), EQ-5D-5L, MARS and BMQ. Whilst checklists are valid measurement tools for assessing inhaler technique (Basheti et al., 2014), they may potentially still be open to subjective interpretation. A potential criticism of this study is that no independent assessment was used to measure the ability of the lead investigator in the PI group and clinic nursing staff in the UC group to assess inhaler technique in a consistent manner, despite the use of the same checklists. However the lead investigator had a thorough understanding on correct inhaler technique (Capstick and Clifton, 2012), and was responsible for training clinic nursing staff on inhaler technique training. Consequently it was considered likely that all inhaler technique assessors were competent in performing this task.

6.2.3.2 Population

The study was adequately powered based on the assumption that an improvement in the ACQ score of >0.5 units could be achieved with the intervention, where a change of 0.5 units describes a clinically important difference in asthma control. This required 38 patients to be followed up for 6-months and assuming a 25% attrition rate, a sample size of 52 patients was required. Indeed 52 patients were recruited, and only five patients were lost to follow-up, which is a particular strength of this study.

This study demonstrated that on average, the ACQ score in patients in the PI and UC groups did not change by more than 0.5 units, and so failed to meet the assumption that the pharmacist interventions would demonstrate a clinically significant change compared to usual medical care. A more conservative estimate of difference of change in ACQ score would have required a larger study, which would not have been achievable within one hospital clinic setting in the time available, since this clinic only managed to recruit 52 patients over a 57-week period.

6.2.3.2.1 Patient selection

Potential participants to be screened for the study were selected through purposive sampling from lists of patients due to attend the difficult asthma clinic. Whilst this may be criticised as it meant that some patients were excluded from being screened for the study, it was also necessary to ensure that patients were not screened who obviously did not meet the study inclusion criteria, including those with other respiratory conditions. This sampling method also reduced the number of patients being screened at each clinic to manageable levels within the time constraints of the clinic. There is a risk that this meant that some patients who were potentially suitable for the study were not invited, but this risk is thought to be minimal since the clinic lists were screened by two people: the lead researcher and clinical supervisor.

A criticism of the study was that asthma was not well defined, and patients were required only to have a clinical diagnosis of asthma and fulfil the criteria for difficult asthma, rather than meeting defined strict objective criteria for asthma

that are used in large high quality randomised clinical trials of drug therapy in asthma. For example in the GOAL study, which used strict criteria for assessing asthma control following drug therapy, the inclusion criteria required 'at least a 6-month history of asthma, a demonstrated improvement in FEV_1 of 15% or more (and > 200ml) after inhalation of a SABA documented within the previous 6 months or as assessed during run-in' (Bateman et al., 2004). These strict criteria ensured that patients were recruited with a diagnosis of asthma and did not have other irreversible causes of obstructive lung disease such as COPD. This present study could not incorporate the same well-defined diagnostic criteria because very few patients attending the local difficult asthma clinic had recent lung function testing with reversibility data available, and it would not have been possible to request this and provide another appointment to attend the clinic at a later date. The broad diagnostic criteria consequently kept participant eligibility wide and aided recruitment to the interventional study. However the risks of participants being recruited to the study having alternative respiratory conditions was considered to be low as all patients had a clinical diagnosis of asthma from a consultant respiratory physician either in the difficult asthma clinic or during a previous hospital admission.

6.2.3.2.2 Asthma phenotypes

It is often considered that patients who are described as having difficult asthma (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014) or severe asthma (Chung et al., 2014), are likely to persist with uncontrolled asthma and remain symptomatic despite maximal therapy, however this may not be true in all cases. The WHO consider that there are three subtypes of severe asthma: (i) untreated severe asthma (due to lack of available or affordable controller treatment), (ii) difficult-to-treat severe asthma, and (iii) treatment-resistant severe asthma (Bousquet et al., 2010). A distinction is made between these three subtypes since patients with difficult-to-treat severe asthma are likely to be less responsive to conventional asthma therapies since they frequently have other factors contributing to their symptoms, including non-adherence, poor inhaler technique, persisting trigger factors or other medical conditions. Those with treatment-resistant severe asthma are unlikely to respond to conventional therapies no matter what interventions are made, and

are only identified by failure to respond to the highest recommended doses of recommended asthma treatments.

Therefore it would be expected that some participants recruited to any difficult asthma study may have treatment-resistant severe asthma and would not respond to interventions that seek to optimise conventional asthma therapies. Consequently responders in studies of difficult asthma would be limited to patients with difficult-to-treat severe asthma and untreated severe asthma. It would therefore be preferable to identify and exclude patients with treatment-resistant severe asthma prior to inclusion in an interventional study, but this would be difficult. This is because treatment-resistant severe asthma can only be identified after optimising therapy and ensuring adherence, which would require a baseline intervention to identify these patients, and thus would mask the impact of any subsequent study interventions. Furthermore, it would not be appropriate to exclude people with treatment-resistant severe asthma from a pragmatic study because these patients would not be excluded from real-life routine treatment.

Diagnostic difficulties are one of the most challenging and complex issues in the management of difficult asthma today, as there is increasing research supporting the concept that difficult asthma has a number of different phenotypes, with different mechanisms driving symptoms, which could respond differently to different classes of medicines (NHS England, 2013). Asthma is often regarded as an allergic airway inflammatory condition mediated by eosinophils and T_H2 immune pathways, which is responsive to corticosteroids. More recently alternative asthma phenotypes based on clinical characteristics, inflammatory processes and triggers have been proposed, such as obesity-associated, smoking-associated, and neutrophilic asthma, which are less responsive to conventional asthma medicines such as ICS (Wenzel, 2012, Bousquet et al., 2010). Whilst current understanding of asthma phenotyping and effective therapies is insufficient to allow individualised treatment in present-day practice, this principle is likely to become increasingly important in the future management of difficult asthma.

It is perhaps understandable that interventional studies in patients with severe or difficult asthma have struggled to demonstrate large benefits in asthma-related outcomes. This study did not seek to, and could not, identify potential asthma phenotypes or the proportion with treatment-resistant severe asthma, it is not known if or how many participants fit into these asthma phenotypes. Whilst asthma control was maintained during this study, these factors may contribute to understanding the reasons why this study did not demonstrate significant improvements in asthma outcomes in either the PI or UC group

6.2.3.2.3 Randomisation methods

This study was designed as a randomised interventional study to ensure that the characteristics of the participants in each group were identical, and a random permuted blocks allocation method was used to prevent imbalance in patient numbers and reduce potential selection bias. The blocks were designed to be small to prevent each group being allocated too many participants at each clinic, because there was only time for two or three patients to be reviewed in each clinic session. Consequently this could have introduced bias into the study, since this meant that permuted blocks of two were used, knowing the next allocation could have affected decisions to recruit patients to the study. However I am confident that this issue did not affect recruitment to the study, because when patients met the inclusion criteria, the decision to enter the study was their own and they were not aware of their allocated study group until after informed consent was obtained.

6.2.3.3 Contamination bias

6.2.3.3.1 Inhaler technique training

Although a checklist was used to determine each study participant's inhaler technique (**Appendix 8**), it should be noted that there was no validation that each clinician assessor could use all inhaler devices correctly. All community pharmacists performing t-MURs had been invited to an asthma education workshop and had received training on correct inhaler technique from the lead researcher, but no assessment or validation had taken place during these sessions. Similarly, nursing staff and physicians who assessed inhaler technique in the UC group had received similar training, but again, there is currently no validated assessment for healthcare professionals to ensure

competence. Therefore there is a risk that even with a checklist, there would still be a certain degree of subjective interpretation of each participant's inhaler technique. This is an issue for most studies assessing inhaler technique since there are currently no widely recognised and validated inhaler technique training programmes for healthcare professionals (Basheti et al., 2014).

This study could have been improved by the design of a formal training package for inhaler technique training and performing a formal assessment of each healthcare professional's competence. This was not feasible as there is currently no validated formal assessment, this would have had to have been produced prior to the study. Furthermore, since data collection took greater than 12 months, to ensure that each community pharmacist was competent, an assessment would have had to be performed prior to each t-MUR visit and funding would have been required to perform this.

Consequently, there is a risk that inhaler technique scores and assessment of optimal, satisfactory and unsatisfactory technique were not consistent between the hospital specialist pharmacist performing baseline assessments in the PI group and follow-up assessments in both groups, or different community pharmacists during t-MURs, or different nursing staff performing baseline assessments in the UC group.

6.2.3.3.2 Case discussion between pharmacist and physicians

One of the ethical requirements of the study protocol was to allow for case discussion between the hospital specialist pharmacist performing interventions in the PI group following their consultations, to ensure that patients were not at a disadvantage from not being reviewed by a physician. Although no data were collected on the content of these case discussions, no concerns were raised. It is possible that these may have led to contamination between the two groups, with physicians providing usual care incorporating interventions described by the pharmacist into their practice, and vice versa.

Contamination of the intervention could have been prevented by the use of two study sites; one providing the pharmacist intervention and one providing usual care. However this was not considered because this would have required a

study operating at two separate hospital Trusts, introducing a number of other variables into the study such as different patient characteristics arising from geographical differences in socioeconomic status or in differences in asthma management strategies and asthma drug formularies. This clearly could have introduced more variability into baseline characteristics than actually occurred in this study.

6.2.3.4 Complex interventions

As discussed in the methodology (**Chapter 4.2**), interventional studies are usually complex in their design, comprising multiple interventions that produce interrelating effects on study outcomes. In the early stages of planning and literature review for this study, it was recognised that studies investigating asthma management provided by pharmacists reported that patients benefited from multiple interventions that included education, medicines optimisation, inhaler technique training, trigger avoidance advice and self-management strategies. Consequently the study design built upon guidance provided by the Medical Research Council on developing and evaluating complex interventions (Craig et al., 2008). Specifically, this study was designed following a thorough literature review of published research that demonstrated how the management of asthma by pharmacists could improve asthma outcomes. This allowed gaps in the literature to be identified, and justify where further research was needed on the management of difficult asthma by pharmacists.

The feasibility of this study and the planned range of interventions to be performed were confirmed as achievable through piloting of the protocol in patients who were subsequently not recruited to the study (Craig et al., 2008). On reflection, it may have been useful to assess the outcome of the intervention at subsequent routine follow-up appointments as a service evaluation of clinical practice, in order to determine the likely impact in these patients. This may have allowed more accurate assumptions to be made of the most practicable interventions to be made within the allocated clinic time slots.

Furthermore, this study may have benefited from external monitoring during the study to ensure that specific interventions were being performed and evaluated correctly (Craig et al., 2008). For example, there was no external validation of

the competence of the pharmacist investigator or healthcare professionals' ability to assess and correct inhaler technique, which would have increased the assurance that the resulting data are valid.

This study was designed as a complex interventional study on the basis that previous studies have demonstrated that single interventional studies in asthma are not as effective as complex interventions (Gibson et al., 2002a, Gibson et al., 2002b), nevertheless some participants raised concerns that the consultations lasted a long time. The precise duration of the clinic appointment was often longer than 90 minutes, but could not be recorded accurately due to the practical difficulties achieving this because the investigator was solely responsible for recruiting and consenting patients, issuing questionnaires to provide baseline and follow-up data, and for performing the consultations in the PI group. There is a risk that the time taken to provide multiple interventions could have disengaged some participants, or that some information could have been forgotten after the consultation. This could have contributed to the lack of effect of the interventions at 6-months, and why inhaler technique was significantly worse at 6-months after being improved during the baseline consultation.

With hindsight, these issues could have been addressed by informing patients of the expected duration of the consultation in the patient information sheet that was posted to them two weeks prior to their appointment, or by greater provision of written patient information following their consultations. This could have been anticipated prior to the study and a range of patient information collated for use within the study. On reflection it should have been anticipated that many participants, who received several interventions might not remember all the information given, especially when some of these such as inhaler technique and education may not be the easiest information to retain in the long-term. Suitable patient information leaflets are available from organisations such as Asthma UK and British Lung Foundation and should have been offered to each patient, or bespoke information could have been written for patients in the study.

There are implications for future practice as reflection on the study procedures may suggest that a range of patient information on asthma, its treatment and inhaler technique guides are made available for patients attending difficult asthma clinics.

A strength of the study design was that there were no mandated interventions, other than checking inhaler technique, which allowed the interventions in the PI group to be tailored to the identified needs of each individual patient as part of a concordant consultation. This could therefore improve the effectiveness of the consultation and avoid the need to provide unnecessary or unwanted interventions. In contrast this lack of structure to the complex interventions might also be considered as a possible failing in the study design, as this may have resulted in inconsistencies in the type of interventions performed; for example not all patients were provided with an asthma action plan. This could have been improved by use of a template designed to ensure a structured consultation that incorporates all the interventions required to form an asthma review. A suitable structure could have been based on the SIMPLE asthma review strategy (Murphy, 2014, Murphy et al., 2012b). This acronym seeks to ensure that all relevant components of a review are discussed including Stop smoking advice, Inhaler technique training, asthma Monitoring, Pharmacotherapy and Medicines optimisation, Lifestyle advice and Education.

6.2.3.5 Data collection

As stated earlier, the outcome measures used in the study were based on the ATS/ERS statement on standardising endpoints for clinical asthma trials and clinical practice (Reddel et al., 2009). Thus the outcome data were appropriate to examine the potential impact of the interventions in routine clinical practice and to compare to other published studies in difficult asthma, although there are some concerns of a lack of consistency in outcome measures used in pharmacist intervention studies.

For the pragmatic reasons discussed in **Chapter 4.8,** data were collected at baseline and six months due to limited time and staff resources. This meant that information on daily lung function using PEF, number of symptom-free days, side effects and daily use of SABA inhaler could not be collected. This could

have provided further information on the patient experience and given greater detail on asthma control to complement the use of ACQ as a measure of asthma control.

It was a potential weakness of the study that asthma control measures such as ACQ were only collected at baseline and six-months, and so were dependent on how participants asthma control was in the fortnight preceding the clinic appointments. This fails to take into account how controlled their asthma was in the weeks and months before this time, and thus demonstrates further how the inability to record asthma symptoms on a daily basis could have adversely affected the study outcomes. In retrospect, it would have been useful to collect data at regular intervals, and the easiest way would have been to be able to incorporate regular follow-up visits. An alternative strategy would have been to ask patients to complete their study questionnaires such as the ACQ, AQLQ(S) and EQ5D-5L at regular intervals, and provided them with stamped addressed envelopes to send back to the lead researcher. However this could have resulted in missing data from participants who may mislay or forget to post back their questionnaires, and the administrative burden for patients could affect recruitment rates.

6.3 Implications for practice

As discussed in the introduction (**Chapter 2.1.5**), the NHS outcomes strategy for COPD and asthma (Department of Health, 2011) and NICE quality standards for asthma (National Institute for Health and Care Excellence, 2013) outline the priority issues in asthma where healthcare professionals should seek to improve the overall management of asthma. The interventions performed and results of this study support both of these national documents and it also addresses gaps in the current understanding of the potential role of pharmacists.

This study has established that the management of patients with difficult asthma through the provision of pharmaceutical care from hospital-based advanced clinical pharmacists is non-inferior to usual medical care in difficult asthma clinics. The increased number of interventions focusing on medicines

optimisation, achieving improvements in adherence and stabilising asthma control in complex cases of difficult asthma demonstrates that pharmacists have a different skill set to doctors, which may be of additional value in difficult asthma clinics. For example, the increase in number of interventions addressing inhaler technique suggests that pharmacists may have greater understanding of the criteria for optimal inhaler technique and may be better at identifying steps in inhaler technique that are performed incorrectly.

Pharmacists are well placed and have the appropriate skills to focus on a number of NICE quality standards (National Institute for Health and Care Excellence, 2013), including providing written personalised action plans (statement 3), training and assessing of inhaler technique (statement 4), performing structured asthma reviews in the community (statement 5), and assessing asthma control (statement 6). This is justified by the fact that these are all areas that pharmacists have addressed in this and other studies, resulting in improved asthma outcomes or non-inferiority to usual medical care.

It is important that commissioners are aware of the beneficial role of pharmacists in difficult asthma services and that specialist pharmacists are encouraged to support difficult asthma services focusing on interventions outlined in the NICE quality standards. The challenge for the pharmacy profession will be to provide commissioners with information on the service specifications for pharmacist-provided care and data on the cost likely to be incurred compared to usual medical care to achieve benefits for patients, although further research may be required to provide this.

Since this study demonstrates that pharmacists can be effective in managing difficult asthma, all pharmacists providing asthma services in primary and secondary care settings should be reassured and encouraged to take a more active role in leading on asthma management. It should be noted that the majority of pharmacist interventions in this study were performed by a hospital-based advanced clinical pharmacist with specialist knowledge and training in respiratory medicine, and so the results may only be applicable to specialist respiratory pharmacists rather than also to non-specialist or community pharmacists.

Overall, the results of this study demonstrate that there are a number of priority areas that should be addressed to improve the management of difficult asthma. These include education of healthcare professionals, incorporation of specialist pharmacists into multidisciplinary difficult asthma clinics, improving the structure and performance of asthma reviews, patient education, medicines optimisation and improving adherence, improving inhaler technique education, and increased uptake of MURs.

6.3.1 Education of healthcare professionals

In order to ensure that pharmacists can implement and support the NICE quality standards for asthma (National Institute for Health and Care Excellence, 2013), education should be prioritised. Standardised and validated healthcare training courses should be developed to facilitate the training of pharmacists and other healthcare professionals in the correct use of inhaler devices.

This is necessary to ensure that pharmacists providing asthma services in secondary care or as part of the MUR service become asthma experts and have the confidence to improve patient care, as the poor uptake of MURs in this study might suggest that some community pharmacists do not feel confident in managing complex cases of difficult asthma.

The lack of validated training packages or courses on inhaler technique is a failing of UK healthcare practice because it is well recognised that the majority of healthcare professionals have poor knowledge on the correct use of different devices (see **Chapter 2.2.4**). Whilst there are inhaler technique guides available, such as from Asthma UK and GINA, and courses for healthcare professionals, such as from The Centre for Pharmacy Postgraduate Education and Simple Steps Education (http://www.simplestepseducation.co.uk), these have not been validated and vary in content.

6.3.2 The role of pharmacists in difficult asthma clinics

Specialist pharmacists should be incorporated into multidisciplinary teams working in secondary care difficult asthma clinics, and this should be a

requirement of the NHS England service specification for severe asthma services (NHS England, 2013).

The 2010 White paper, *Equity and excellence*, recognised that “pharmacists, working with doctors and other health professionals, have an important and expanding role in optimising the use of medicines and in supporting better health“ (Department of Health, 2010). This assertion is supported by the findings of this study, which has established that the provision of pharmaceutical care from hospital-based advanced clinical pharmacists to patients with difficult asthma is non-inferior to usual medical care.

Pharmacist-led services may be cheaper than consultant physician-led services in terms of staff costs, and could free up consultant physician time for other complex tasks that others could not perform within the NHS England service specification for severe asthma services (NHS England, 2013).

6.3.3 Format of asthma reviews

This study did use a protocol to aid asthma reviews in the PI group (**Appendix 7**), and may provide advantages in clinical practice by ensuring that all recommended components of an asthma review are addressed. An alternative, but similar method previously recommended to aid pharmacists about how to manage asthma is to use the acronym SIMPLE as an aid to remembering the main components of asthma reviews during clinic consultations or MURs (Murphy, 2014, Murphy et al., 2012b). Variants of this have been recommended to GPs (Ryan et al., 2013). SIMPLE stands for Stop smoking, Inhaler technique, Monitoring, Pharmacotherapy, Lifestyle and Education.

Monitoring of asthma control should be performed regularly by pharmacists as part of asthma reviews in primary and secondary care, or to identify patients who may require a t-MUR. Assessing asthma control is a quick and simple task to perform, and can be achieved through a variety of quick and validated tools such as ACQ or the ACT (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). These are often given to patients to complete before hospital clinic appointments as a review assessment, but can also be given by community pharmacists to patients whilst they wait for their

prescription to be dispensed as this may assist in identifying which patients to target for asthma MURs.

Healthcare professionals may benefit from training on consultation styles such as CBCT and motivational interviewing techniques, since these have been demonstrated to improve adherence in patient populations with both difficult asthma (Gamble et al., 2011) and other long term conditions (Easthall et al., 2013). However these consultation styles are time and labour intensive, with one study in difficult asthma requiring up to eight individual intervention visits over a 12-week period (Gamble et al., 2011), whilst other studies described in one systematic review ranged from a one-off 30 minute session up to four hours divided over multiple visits (Easthall et al., 2013). In the current study, none of the healthcare professionals in either group had received prior training on these counselling techniques, and there was insufficient time within the clinic appointments to dedicate to these techniques.

6.3.4 Patient education

All patients should be provided with self-management education and offered an asthma action plan, such as those available from Asthma UK or the Primary Care Respiratory Society, as this improves health outcomes (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014). In addition, patients should be provided with written information on asthma, such as patient information leaflets provided by Asthma UK and the British Lung Foundation, or from the NHS Choices website. These may be useful to reinforce education provided to patients during asthma consultations

Although smoking cessation support was an uncommon intervention in this study as only 3 patients in each study group were current smokers, all asthma patients who are currently smoking should be offered nicotine replacement therapy or other drug therapy and referral to local stop smoking services. This is an important healthy living intervention and should be foremost in all patient contacts as smoking has been associated with worsening asthma control, increased exacerbations and increased risk of mortality (Ryan et al., 2013).

Similarly, the lifestyle of asthma patients should form part of asthma reviews and MURs, with particular regards to identifying and avoiding triggers for worsening asthma control, as well as providing healthy living advice including diet, exercise, weight management and alcohol since each of these can adversely affect asthma control (British Thoracic Society and Scottish Intercollegiate Guidelines Network, 2014, Ryan et al., 2013).

6.3.5 Medicines optimisation

Pharmacists should use their skills routinely to ensure that medicines are prescribed used correctly, by optimising treatment regimens, stepping up or stepping down treatment as necessary, and assessing adherence.

6.3.6 Adherence

Adherence to ICS is well recognised to be highly variable amongst asthma patients, and this study found that more than half of participants had adherence rates less than 80% and a more than a third had adherence rates less than 50%, and nearly one in five had adherence rates exceeding 100%. Community pharmacists are well placed to monitor adherence using prescription refill rates, and should use these data proactively to identify potential non-adherent patients and target these for MURs, since this may improve asthma control and allow a reduction in prescribed ICS dose if taken regularly (Khachi and Karikari, 2013).

There is a clear need for primary care healthcare professionals, including GPs, practice nurses and primary care pharmacists to review adherence data as part of annual asthma reviews, especially in patients with uncontrolled asthma. Furthermore there should be easy access to GP prescribing data in difficult asthma clinics at hospitals.

6.3.7 Inhaler technique

Pharmacists, and other healthcare professionals in all sectors should check and optimise inhaler technique regularly at every patient contact, whether during hospital admissions, clinic appointments, asthma reviews, MURs, or when collecting prescriptions.

Inhaler technique in this study was poor amongst participants in both groups for all devices, with many making critical errors that would be expected to substantially reduce the effective dose received, and thus reducing the clinical efficacy of ICS. Whilst inhaler technique was improved during the baseline consultations, this was not maintained by six-months, and indeed was not maintained by two months in the six participants who had a t-MUR. This highlights the importance of rechecking inhaler technique soon after it has been optimised, and regularly thereafter.

Since inhaler technique was poor throughout the study, this again highlights an urgent need for standardised and validated inhaler technique checklists to be developed to aid the assessment and optimisation of patients' inhaler technique.

6.3.8 MURs

This study was designed to provide co-ordinated pharmaceutical care between primary and secondary care pharmacists to ensure that all participants in the PI group received follow-up consultations with new and reinforced interventions in attempt to optimise medical management of difficult asthma. A pilot study preceding this study had found that there were further opportunities for community pharmacists to provide support for asthma patients since two thirds of patients attending the difficult asthma clinic, who were eligible, had not been offered a MUR (Capstick et al., 2012). Therefore the MUR service was chosen as an opportunity to provide this co-ordinated pharmaceutical care because the community pharmacy MUR service is well established (Blenkinsopp et al., 2007, Blenkinsopp et al., 2008, The Cambridge Consortium, 2012). However this study experienced difficulties achieving shared care between secondary and primary care pharmacists due to poor uptake of t-MURs partly resulting from an apparent miscommunication between community pharmacists and patients.

Community pharmacists should aim to increase the number of MURs offered to patients with difficult asthma, which may be achieved by identifying patients prescribed high ICS doses, frequent prescriptions for SABAs and using ACQ or ACT questionnaires. Improved education of community pharmacists may increase their knowledge, skills and confidence in providing MURs to patients

with difficult asthma, where their condition and treatment appears to be very complex.

7 Conclusions and recommendations for future work

7.1 Conclusions

The aim of this research study was to investigate the effects of a co-ordinated management strategy between primary and specialist secondary care pharmacists on asthma control and quality of life in patients with difficult asthma. This study is the first to investigate the effects of a redesigned pharmaceutical pathway across the primary and secondary care interface in patients with difficult asthma, and the first to compare pharmaceutical management of asthma to usual medical care.

Three literature searches were performed to evaluate published studies examining the effects of (i) complex pharmacist interventions, (ii) inhaler technique, and (iii) interventions to improve adherence, on asthma control, and a review of research study design was undertaken. This facilitated the decision to design a pragmatic six-month, prospective, randomised, open trial to compare the management of patients with difficult asthma by a hospital-based specialist advanced clinical pharmacist with follow-up t-MUR from community pharmacists, to usual medical care. A sample size calculation required 52 patients to be recruited to demonstrate a clinical and statistically significant difference in ACQ score between the two study groups assuming a 25% attrition rate. This study was successful in recruiting 52 patients, of whom 47 were followed up for six-months, and consequently this study was adequately powered for the primary outcome measure of ACQ score.

This study recruited a representative sample of patients with difficult asthma who were uncontrolled, requiring frequent emergency courses of OCS to treat asthma exacerbations, and were high users of SABA inhalers. The interventions provided to participants randomised to the PI group were individualised according to their identified needs, and were based on current published evidence to ensure that they were likely to have benefits to each patient. The outcome measures used in this study were appropriate for use in this study, as they are relevant to routine clinical practice and are recommended endpoints for clinical asthma trials (Reddel et al., 2009).

In contrast, a major limitation of the study was that only six of the 26 participants in the PI group received a t-MUR from their usual community pharmacist, despite receiving a written and verbal referral. Consequently few participants in the PI group received the full protocol interventions or received reinforcement of the interventions provided in the initial baseline consultation.

Participants in the PI group received significantly more interventions at the baseline consultation in the hospital difficult asthma clinic than participants in the UC group, reflecting the ability of pharmacists to identify unmet health needs in patients with difficult asthma.

At six-months, the provision of pharmaceutical care from hospital-based advanced clinical pharmacists to patients with difficult asthma was non-inferior to usual medical care for the primary outcome measure of ACQ, and also for all other asthma outcomes measured, including quality of life, inhaler technique and overall adherence. Asthma control and quality of life was stabilised in both study groups, with low rates of exacerbations and hospital admissions, which can be regarded as a positive outcome in a study of patients with difficult asthma who generally

Inhaler technique at baseline was poor in all participants, which was likely due to the fact that fewer than half of participants had previously received inhaler technique training by primary care healthcare professionals. Inhaler technique was improved with education at baseline in both study groups, but this was not maintained in either group. It is likely that patients should receive regular and repeated reinforcement of correct inhaler technique to ensure they maintain correct inhaler technique in the long-term.

Adherence to ICS treatment was poor in both study groups and patient self-reported adherence under-estimates adherence according to prescription data. Just over half of participants had sub-optimal ICS adherence (defined as adherence rates less than 80%), and approximately one-third of participants collected less than half of their ICS prescriptions. In this study, there was a greater increase in the proportion of patients with adherence rates 80-120% in the PI than the UC group over the six-month study period, demonstrating that

the pharmacist had a greater impact on adherence than physicians. As poor ICS adherence should adversely affect asthma control, there is a need for primary care healthcare professionals including GPs, practice nurses and pharmacists to review adherence data, especially in participants with poor asthma control.

This study has provided proof of concept that the management of patients with difficult asthma can be adequately provided by an advanced clinical pharmacist with a specialist interest in respiratory medicine, as an alternative to usual medical management. Complex interventions provided by a pharmacist that incorporates asthma monitoring, inhaler technique training, medicines optimisation and adherence counselling, education, asthma action plan provision, and healthy living advice are useful in stabilising difficult asthma and preventing exacerbations.

7.2 Recommendations for future research

The main unanswered questions arising from this study stem from the fact that the majority of participants in the PI group did not have a t-MUR and so did not receive any follow-up interventions. Consequently it is not known whether following up baseline consultations in hospital difficult asthma clinics with t-MURs would achieve additive benefits on asthma outcomes, inhaler technique or adherence. It is recommended that future research should examine whether t-MURs can achieve additional benefits in difficult asthma following the initial pharmacist consultations in order to support and build on improvements in medicines use. If t-MURs are not well used or effective in supporting the initial hospital consultation for patients with difficult asthma, research could investigate support provided by GPs, practice nurses or primary care practice-based pharmacists.

Research should be undertaken to determine the optimum frequency of follow-up consultations that are required to maintain optimal inhaler technique and adherence.

Since adherence was poor for many patients, strategies to enhance the identification of poor adherence in primary care and secondary care difficult asthma clinics should be studied. The effect of increased reviews of adherence data in difficult asthma should be investigated to determine whether this improves overall adherence and asthma outcomes.

There are a number of novel inhaler devices, which may be easier to use than existing devices that have been launched for use in asthma in 2104 including Ellipta, Nexthaler and Spiromax. Research should be undertaken to investigate patients' preference for these devices over existing alternatives in an independent study, and whether these devices will improve adherence and inhaler technique, and how this might impact on asthma control.

8 Appendices

Appendix 1. Characteristics of included studies: Effect of complex pharmacist interventions on asthma control

Criteria for judging bias is based on the Cochrane handbook for systematic reviews (Higgins and Green, 2011).

Armour et al., 2007

Methods	Six-month, multi-site, randomised intervention versus control repeated measures study, in Australia.
Participants	**Population**: 50 community pharmacies recruited 396 patients (Pharmacist Intervention [PI]: 191; Usual Care [UC]: 205). **Baseline characteristics**: In the PI group, mean age 47.5 years, FEV_1 79.3% predicted. 88.0% have severe asthma symptoms, 9.4% have moderate symptoms. 87.2% were taking a preventer + reliever ± LABA, 12.8% were taking a reliever only. In the UC group, mean age 50.4 years, FEV_1 75.4% predicted. 70.8% have severe asthma symptoms, 27.7% have moderate symptoms. 84.3% were taking a preventer + reliever ± LABA, 15.7% were taking a reliever only. **Inclusion criteria (Pharmacies)**: Community pharmacies had to have Quality Care Pharmacy Program accreditation in Australia, compatible computer system to use spirometer software, have a minimum of two pharmacists on duty at all times who must have attended a study training session. **Inclusion criteria (Patients)**: Adults aged 18-75 years, with a previous diagnosis of asthma, and fulfil 1 or more of the revised Jones' Morbidity Index subcriteria demonstrating uncontrolled asthma (within the past 4 weeks: use of reliever inhaler >3 times a week, nocturnal or early morning symptoms, time off work/study because of asthma, and no visits to a doctor because of asthma within the past 6 months. **Exclusion criteria (Pharmacies)**: Community pharmacies were excluded if they were currently involved with any other research project. **Exclusion criteria (Patients)**: Terminal illness, current enrolment within another clinical trial, do not self-administer inhalers, do not speak English well enough to complete questionnaires or communicate with pharmacists.
Interventions	1. Pharmacists in the PI group were given an asthma education manual and were trained on risk assessment, pathophysiology of asthma, asthma medications, National Asthma Council six-step asthma management plan, patient education, goal setting, adherence assessment, spirometry (by qualified respiratory scientists), during a 2-day workshop delivered by the research team. The intervention provided to patients was the Pharmacy Asthma Care Program protocol, specifically assessing asthma control, targeted counselling and education on asthma, medication and lifestyle issues, review of inhaler technique, adherence, detection of drug-related problems, goal setting and referral to GP as appropriate. This was reinforced at 1-month, and again at 3-months if necessary. 2. Pharmacists in the UC group were trained on risk assessment, spirometry and the control protocol only. Patients in the UC group received no intervention, except from the pharmacist's usual care.
Outcomes	The primary outcome measure was change in overall asthma severity/control, as assessed using the Australian National

	Asthma Council asthma severity assessment table. At 6-months, the proportion of patients who were classified as having severe asthma declined significantly in the PI group (87.9% to 52.7%, p<0.001), whilst that of the UC group remained unchanged (71.2% to 67.9%, p=0.11), associated with an odds ratio for reduced proportion of patients with severe asthma in the PI group of 2.68, 95% CI 1.64 to 4.37; p<0.001). There was a greater improvement in health status in PI vs. UC group, with a mean difference in improvement in AQLQ of 0.23, p<0.05.	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Pharmacists providing PI or UC were randomly assigned to either group, but sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation of community pharmacists to PI or UC group was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Risk of detection bias due to unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Power calculation reported, and attrition rate (PI:13.6%, UC 9.3%) was within acceptable limits (25%).
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but all data reported for patients in both groups.
Other bias	Low risk	The study appears to be free if other sources of bias.

Barbanel et al., 2003

Methods	Three-month, randomised controlled study, in London, England.
Participants	**Population**: 24 adults (Intervention group: 12; Control group: 12). **Baseline characteristics**: Mean (SD) age 45 (17) in the intervention group and 47 (17) in the control group. **Inclusion criteria**: Age 18-65 years with a GP diagnosis of asthma, who were using ICS. **Exclusion criteria**: Recent attendance at secondary care hospital with acute asthma, change in asthma treatment within 6 weeks, acute respiratory infection.
Interventions	The community pharmacist attended a 3-day multidisciplinary course on asthma care. Patients in the intervention group received education, assessment of inhaler technique, and self-management advice based on PEF measurements and symptoms, with weekly telephone follow-up. Patients in the control group received no input from the pharmacist.
Outcomes	Outcome measure used the 'North of England asthma

	symptoms scale' - a validated instrument measuring asthma related health status, where a 6-point reduction in score indicates a significant improvement in asthma. In the intervention group, a significant improvement in symptom scores was observed (26.3 to 20.3, mean improvement = 6 [clinically meaningful improvement]). In the control group, there was a worsening of symptom scores (27.8 to 28.1). Overall, there was a significant improvement in patients in the intervention compared to the control group (difference adjusted for baseline scores = 7.0 [95% CI 4.4 to 9.5] p<0.001).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomised using sealed envelopes.
Allocation concealment (selection bias)	Unclear risk	Patients were randomised using sealed envelopes, but method of allocation / selection of envelopes was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No description of blinding, except that Control group received no input from the pharmacist.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All patients completed questionnaires with no input from the pharmacist.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One control patient lost to follow-up. No power calculation performed.
Selective reporting (reporting bias)	Low risk	Low risk. Data reported for patients in both groups.
Other bias	Low risk	The study appears to be free if other sources of bias.

Charrois et al., 2006

Methods	Six month, prospective, randomised controlled study, in rural Alberta, Canada.
Participants	**Population**: Five trained community pharmacies recruited 70 patients (36 in the intervention group, 34 in the usual care group). 9 patients (2 in the intervention group) did not complete the 6-month study. **Baseline characteristics**: Mean ± SD age was 35.7 ± 10.2 years in the intervention group and 38.7 ± 10.7 years in the usual care group. Significantly fewer patients were assessed as having adequate inhaler technique in the intervention group (66.7% vs. 88.2%, p<0.05). Patients in the intervention and control groups had similar baseline asthma control (Mean ± SE) ACQ 1.45 (0.19) vs. 1.91 (0.18) respectively, and a similar proportion were prescribed ICS (69.4% vs. 76.5%). **Inclusion criteria**: Adults aged 17-54 years with a self-reported diagnosis of asthma, and considered at high risk (defined as an emergency department visit or hospital admission due to asthma in the previous 12 months or use of >2 canisters of inhaled beta$_2$-agonist in the previous 6 months.

	Exclusion criteria: Inability to understand English, patients who do not administer their own medicines, were not available for 6-month follow-up, or did not provide consent.
Interventions	Patients in the intervention group were received an educational program on asthma, action plan, assessment of asthma therapy, and referral to a respiratory therapist and primary care physician as needed. Patients were followed up at followed up at 0, 0.5, 1, 2, 4 and 6 months. Patients in the usual care group received an asthma education booklet and general advice as needed. Patients were followed up at 0, 2, and 6 months.
Outcomes	The primary objective was change in ACQ. The mean change in ACQ at 6 months was 0.33 for the control group (standard error [SE] 0.17) and 0.43 in the intervention group (SE 0.15) ($p = 0.66$). There was no significant difference in change in ACQ between the two groups. There was no significant difference between the two groups for any of the secondary outcomes: emergency department visits, hospital admissions, use of inhaled or OCS or lung function using FEV_1. Compliance with intervention was poor: only 75% of the intervention group received an action plan, fewer than half had education at each visit, more than half had no recommendations made to improve asthma control.

Risk of bias

Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Internet randomisation service provided by the Epidemiology Coordinating and Research (EPICORE) Centre and the Centre for Community Pharmacy Research and Interdisciplinary Strategies (COMPRIS) at the University of Alberta.
Allocation concealment (selection bias)	Low risk	Central allocation methods were used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Power calculation reported (in a prior publication), and attrition rate (13%) was within acceptable limits (29%).
Selective reporting (reporting bias)	Low risk	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Cordina et al., 2001

Methods	12-month randomised controlled longitudinal, prospective trial,

	in Malta.	
Participants	**Population**: 22 community pharmacists (11 trained to provide the intervention, and 11 untrained for the control group). 152 patients were recruited (86 in the intervention group, and 66 in the control group. **Baseline characteristics**: Mean age 41.3 ± 18.35 years in the intervention group and 45.88 ± 18.11 years in the control group. The mean PEF was 374.93 ± 134.08 L/min in the intervention group and (390.12 ± 137.91 L/min in the control group. **Inclusion criteria**: Adults and adolescents aged 14 years and older, who were registered at an asthma clinic. **Exclusion criteria**: Other significant pulmonary disease or condition that would hinder PFT performance or completion of questionnaires.	
Interventions	Patients in the intervention group received a comprehensive asthma education and monitoring program, including information on asthma pathology, triggers, use of inhaler devices and peak flow meters using verbal counselling, educational video, information leaflet, and subsequent monitoring and reinforcement. Follow-up occurred at monthly intervals. Patients in the control group received routine dispensing only.	
Outcomes	At 12 months, there was no difference in health-related quality of life using SF-36 between the two groups (data not reported), however using the LWAQ, patients in the intervention group reported better quality of life than patients in the control group at 12 months (0.96 ± 0.38 vs. 1.03 ± 0.036 at baseline, p=0.044), but this was not significantly different from the control group using repeated-measures ANOVA using age and gender as covariates. At 12 months, the mean PEF was significantly lower than at baseline in patients within the control group (for 55 patients where data were available, from 377 ± 131 L/min to 340 ± 115 L/min, p=0.009), but was unchanged in the intervention group (data not reported). There was no significant difference in the number of GP visits or number of days of work or school lost. Significantly more patients in the intervention group improved their inhaler technique over the 12-month study duration than in the control group (40/64 vs. 24/55, p<0.001).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Pharmacists providing PI or UC were randomly assigned to either group, but sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation of community pharmacists to PI or UC group was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded assessments.
Incomplete outcome data	Unclear risk	Sample Size calculation not

(attrition bias) All outcomes		specified. 119 (of 152 [78%] patients completed study.
Selective reporting (reporting bias)	High risk	Complete data on the first outcome measure SF-36 was not reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Garcia-Cardenas et al., 2013

Methods	6 month cluster randomised controlled trial, in Spain.
Participants	**Population**: 33 community pharmacies were trained to provide the intervention (29 took part in study) and 32 untrained community pharmacies were recruited for the control group (22 took part in the study). 373 patients enrolled, 346 patients completed, but one pharmacy data excluded from analysis due to lack of reliable data, therefore 336 patients were available for analysis (186 in the intervention group, 150 in the control group). **Baseline characteristics**: Mean (SD) age was 55.8 (19.1) years. Mean (SD) ACQ was 1.4 (1.1) and 1.3 (1.2) in the intervention and control groups respectively, however significantly fewer patients in the intervention group had controlled asthma (28% vs. 42.7%, p=0.005). **Inclusion criteria**: Adults aged 18 years or older with a physician diagnosis of asthma. **Exclusion criteria**: Participation in other asthma education programs, pregnancy, communication difficulties, suffering from seasonal asthma, or other pathologies such as COPD, lung cancer, RTIs or terminal illness.
Interventions	Patients recruited to the intervention group received a protocol-based intervention addressing individual needs related to asthma control, inhaler technique and adherence. Patients also received education using verbal and written instructions, and physical demonstration of Turbohaler use. Patients recruited to the control group received no intervention other than their pharmacist's usual care (usually the safe supply of medicine use and advice about taking medicines). All patients in the intervention and control groups had three scheduled visits to the pharmacy, although intervention patients could have up to six visits if needed.
Outcomes	At six months, there was a clinical and statistically significant improvement in asthma control in the intervention group (ACQ -0.66, p<0.001), but not in the control group (-0.15 (p value not reported)). The mean difference between the groups in adjusted mean changes for ACQ from baseline to final visit was -0.18 (IC95% -0.37 to 0.02), p=0.079 in patients who had controlled asthma at baseline, and -0.62 (IC95% -0.80 to -0.43), p<0.001 in patients who had uncontrolled asthma at baseline. Turbohaler inhaler technique improved in the intervention and control groups from baseline to 3-month intermediate visits, but only from Intermediate to final 6-month visit in the intervention group. The proportion of patients with correct inhaler technique at 6 months was significantly higher in the intervention group compared to the control group (75.8% vs. 50.0%, p < 0.001). The proportion of patients who were found to be adherent to treatment at 6 months was significantly higher in the

	intervention than in the control group (78.5% vs. 52.0%, p < 0.001).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pharmacists /Pharmacies providing intervention or control were randomly assigned to either group, using a computer-generated list of random numbers with a 1:1 ratio of pharmacies.
Allocation concealment (selection bias)	Low risk	Allocation of pharmacies to intervention or control group performed by computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study required 342 patients assuming a 20% attrition rate. 336 completed the study, which was therefore within acceptable limits.
Selective reporting (reporting bias)	High risk	10 patients in the control group from one pharmacy were excluded from analysis due to lack of reliable data.
Other bias	Low risk	The study appears to be free if other sources of bias.

Kritkos et al., 2007

Methods	12-week parallel group pilot study, with repeated measures design, in Sydney, Australia.
Participants	**Population**: Five trained community pharmacists providing the intervention, one trained pharmacist researcher, and two untrained community pharmacists providing usual care. 48 patients were recruited (16 to the intervention provided by community pharmacist group (Group A), 16 to the intervention provided by pharmacist researcher group (Group B), 16 to the usual care provided by community pharmacist (Group C). **Baseline characteristics**: Mean ± SD age was 49.5 ± 20.6 years, 56.9 ± 19.4 years and 46.4 ± 20.6 years in Groups A, B, and C respectively. The percentage of patients with severe asthma symptoms at baseline was 56%, 44% and 50% in Groups A, B and C respectively. There were no significant differences in medication use between Groups A, B, and C regarding ICS use (25%, 25%, and 19%), or combination therapy (75%, 75%, and 81%), respectively. **Inclusion criteria**: Age over 16 years, with a previous self-reported diagnosis of asthma, assessed as uncontrolled using the Revised Jones Morbidity Index for asthma assessment, who could use a preventer medication, and could read and understand English **Exclusion criteria**: Self-reported diagnosis of COPD, unable

	to use inhaler, or under on-going GP review within a 3+ Visit plan.
Interventions	The intervention provided by trained community pharmacists and the pharmacist researcher comprised education on asthma, its management, asthma medication, inhaler use, and relevant written information. Patients provided with usual care from their community pharmacists received the same written information, but had no additional education. Follow up was provided at 6 and 12 weeks.
Outcomes	No primary outcome measure was specified. There was an improvement in inhaler technique; for the pMDI: the proportion of patients in groups A and B with optimal pMDI technique improved from 9% and 14%, respectively, at baseline to 82% and 93% respectively, at 12 weeks (n = 11, p =0.02; n = 14, p < 0.001). For the DPI: the proportion of patients in Groups A and B with optimal DPI technique improved from 9% and 14% respectively at baseline to 82% and 93% respectively at 12 weeks (n = 11, p =0.02; n = 14, p < 0.001). There was no significant improvement in pMDI or DPI technique in control group. At baseline the proportion of patients with severe asthma/poor control was 56%, 44% and 50% in Groups A, B and C respectively; at 12 weeks there were significantly fewer patients in Groups A and B with severe asthma/poor control (25% and 13%) than in Group C (50%), p=0.04). There were also significant improvements in quality of life (measured as change in AQLQ) in Group A (change in mean score 1.1; p=0.03) and Group B (change in mean score 1.8; p=0.003) over 12 weeks, but not in Group C (change in mean score 0.0). There were also small, but significant improvements in adherence using the MARS in Groups A and B, although adherence was reported to be high at baseline. There was a significant increase in asthma knowledge post-education and at 6 and 12 weeks in Groups A (p<0.001) and B (p<0.001), but there was no significant change in Group C.

Risk of bias

Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation of Pharmacies to Group A, B or C not described.
Allocation concealment (selection bias)	Unclear risk	Allocation of community pharmacists to each group was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	100% retention rate.
Selective reporting (reporting bias)	Low risk	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Mehuys et al., 2008

Methods	Six-month randomised, controlled, parallel-group trial, in Belgium	
Participants	**Population**: 66 trained community pharmacists recruited 201 patients (107 in the intervention group and 94 in the control group. **Baseline characteristics**: Mean age 35.2 years and 36.3 years in the intervention and control groups respectively. Baseline morning PEF was 409.7 L/min and 390.7 L/min respectively. Mean ACT score at baseline was 19.7 and 19.3 in the intervention and control groups respectively. 89.5% of intervention patients, and 93.9% of control group patients were taking either a ICS/LABA or ICS only inhaler at baseline. **Inclusion criteria**: Age 18-50yrs, treated for asthma at least 12 months, using controller medication, and regular visitor to community pharmacy. **Exclusion criteria**: Smoking history >10pk years, other severe disease or ACT <15 or =25	
Interventions	Patients in the intervention group received education on inhaler technique, asthma symptoms, triggers and warning signs, understanding medication, adherence and smoking cessation, with follow-up advice at 1- and 3-months if ACT still sub-optimal. Patients in the usual care group received usual pharmacist care.	
Outcomes	150 patients (75%) completed the study. Mean ACT was unchanged in both groups (However, in patients with insufficiently controlled asthma at baseline, the mean change from baseline was +2.3 and +0.3 in the intervention and control groups respectively, mean difference 2.0 [95% CI 0.1-3.9] p=0.038)). There was no significant difference in the AQLQ. There was a significant decrease in rescue medicine use at 3 and 6 months in the intervention vs. control group (at 6 months -0.57 vs. -0.43 inhalations per day, p=0.012). Adherence by prescription refill rates was higher in the intervention vs. control group (90.3% vs. 74.6%, p=0.016). Significantly more patients had optimal (100%) inhalation technique at 6 months in the intervention group (increase of 40% to 64.3%, vs. a 20% increase to 36.5% in the control group.	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence allocation predetermined by the investigators based on a randomisation table.
Allocation concealment (selection bias)	Low risk	Serially numbered, closed envelopes were made for each participating pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Each community pharmacy could have intervention and control patients. Intervention known
Blinding of outcome	High risk	Unblinded assessments.

assessment (detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Power calculation reported, and attrition rate (25%) was within acceptable limits (30%).
Selective reporting (reporting bias)	Low risk	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Petkova, 2008

Methods	Four-month, prospective, randomised controlled trial, in Bulgaria.	
Participants	**Population**: 10 trained community pharmacies. 50 adults (22 in the intervention group, 28 in the control group). **Baseline characteristics**: Mean age was 35.14 years and 40.82 years in the intervention and control groups respectively. Three of the 22 patients in the intervention group had moderate to severe persistent asthma (according to Expert Panel Report 2: Guidelines for diagnostic and management of asthma, 1997) at baseline, compared to 12 of 28 in the control group. **Inclusion criteria**: Age >14 years with a diagnosis of bronchial asthma and understanding of spoken and written Bulgarian. **Exclusion criteria**: Presence of other significant pulmonary disease (e.g. carcinoma), presence of any condition that would hinder completion of questionnaires (e.g. poor eyesight or literacy).	
Interventions	The intervention comprised a community pharmacy-based educational program on asthma, triggers, exercise, self-management, smoking-cessation, treatment, inhaler technique, and side effects. Patients were followed-up on three occasions. The control group received usual care from their pharmacy, with no additional information provided.	
Outcomes	No primary outcome measure was specified. At 4-months, quality of life (measured using patients' subjective opinions assessed using an Asthma Assessment Form: 1 = interference all of the time, to 5 = interference none of the time) was increased in the intervention group (from 3.55 ± 1.355 to 3.77 ± 1.020, p<0.0001), but was reduced in the control group (from 3.39 ± 0.685 to 3.00 ± 0.903; p=0.039). There was no significant effect on lung function using PEF rate. Inhaler technique data is not presented in a manner to make conclusions on the clinical impact of good or poor inhaler technique.	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Random sequence generation not specified. However 'the separation is based on patient willingness to take part in the education program.' This may bias the recruitment process.
Allocation concealment (selection bias)	Low risk	Random numbers used.

Blinding of participants and personnel (performance bias) All outcomes	High risk	Likely no blinding. Unclear if any blinding occurred in any form - unclear if each pharmacy had intervention and control patients.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded assessments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients appear to have completed the 4-month study, but no Power calculation.
Selective reporting (reporting bias)	Low risk	All data reported.
Other bias	High risk	Inhaler technique assessment does not specify inhaler devices, and scoring method does not adequately indicate clinical impact of poor technique.

Saini et al., 2008

Methods	Six-month, parallel group, controlled repeated measures research design study in New South Wales, Australia
Participants	**Population**: 12 community pharmacists trained to provide asthma intervention to 51 patients, and 8 untrained pharmacists to provide usual care to 39 patients. 90 patients in total (83 patients completed the study: 46 in the intervention group and 37 in the control group. **Baseline characteristics**: Mean age ± SD was 50.8 ± 15.3 years in the intervention group and 50.4 ± 18.4 in the control group. Asthma severity score (using the National Asthma Council's asthma severity classification; range 5-15 [5=mild; 5=severe]) was 11.4 ± 2.8 and 10.3 ± 3.2 respectively. **Inclusion criteria**: Asthma patients who use their bronchodilator more than three times a week, frequent exacerbations, or patients who expressed general concerns over their asthma. **Exclusion criteria**: Age under 12 years, other major disease or terminal illness.
Interventions	The intervention comprised intensive pharmacist education (assess asthma severity, medication and inhaler use, perform spirometry, provide Action Plan, and education, and make appropriate interventions). Patients were followed up at 1-, 4- and 6-months. The control group comprised standard practice in community pharmacies. Patients were followed up at 6-months.
Outcomes	At 6 months: Asthma severity Score (range 5-15 [5=mild; 5=severe]) showed a significant decrease (improvement) in intervention group compared to the control group (3.6 vs. 0.09; $p<0.001$ in the as per protocol results. This remained statistically significant in the intention to treat analysis ($p<0.001$). There was a significant reduction in the risk of non-adherence (-1.8 vs. -0.6 in the intervention vs. control groups, $p=0.01$ on a Brief Medication Questionnaire scale 1-11 [1=low risk of non-adherence, 11 = high risk}, although baseline score was 3.0. There was no significant difference in change in quality of life

	scores or salbutamol use in the intervention and control groups.	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Pharmacists providing PI or UC were randomly assigned to either group, but sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Allocation of community pharmacists to PI or UC group was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Power calculation took into account potential attrition rate and clustering effect from Pharmacies
Selective reporting (reporting bias)	Low risk	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Appendix 2. Characteristics of included studies: Effect of inhaler technique training on asthma control

Criteria for judging bias is based on the Cochrane handbook for systematic reviews (Higgins and Green, 2011).

Al-Showair, 2007

Methods	Six-week, randomised controlled trial, in English hospitals.	
Participants	**Population**: 108 adult asthma patients (107 completed). 36 patients recruited to the Good Technique [GT] control arm (good peak IFR on baseline testing, after extended screening following the completion of recruitment to the intervention arm); 36 received Verbal Training [VT] (1 drop out) and 36 received verbal training plus 2Tone trainer Inhaler [2T]. **Baseline characteristics**: Mean age 52.6 to 60.4 years, mean FEV_1 62.2 to 76.9% predicted. Mini-AQLQ 3.7 to 3.9. **Inclusion criteria**: Patients with asthma attending an outpatient clinic, treated with ICS via a pMDI without a spacer. **Exclusion criteria**: Asthma exacerbation within the past four weeks, deafness, or inability to distinguish between the one and two tones of the 2Tone trainer inhaler, poor co-ordination using a pMDI.	
Interventions	It is unclear who performed the intervention in this study. Measurement of peak IFR using In-Check DIAL, and assessment of pMDI inhaler technique. Patients with good inhaler technique (good co-ordination and slow peak IFR (<90 L/min) were placed in the good technique (GT) control group. Patients with a fast peak IFR (>90 L/min) were randomised to either verbal training (VT) or verbal training plus provision of a 2Tone trainer inhaler (2T). Follow up at 6 weeks.	
Outcomes	All 36 GT patients had peak IFR <90L/min at baseline and at six-weeks. At six weeks, there was a significant increase in the proportion of patients who had an appropriately slow (<90 L/min) inspiratory flow rate through a pMDI in both the VT (increased from 0 to 23/35 [66%], p<0.001) and 2T groups (increased from 0 to 35/36 [97%), p<0.001). Mean peak IFR at week 6 was 70.0, 80.0 and 50.0 for the GT, VT and 2T groups respectively. Mean change in peak IFR could not be calculated as the In Check was calibrated only up to 120L/min and many of the VT and 2T patients had peak IFRs >120L/min at Baseline. At week 6, no GT patients had a change in AQLQ >0.5; 14 VT patients had a change >0.5 and 3 >1; 22 2T patients had a change >0.5 and 8 >1. Only patients in the 2T group perceived an improvement in asthma control based on a 5-point Likert scale (an un-validated assessment).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear Risk.	Patients with fast peak IFR randomly allocated, but method of randomisation was not described.

Allocation concealment (selection bias)	High Risk.	Allocation method not described.
Blinding of participants and personnel (performance bias) All outcomes	High Risk.	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High Risk.	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	Low Risk.	Power calculation required 30 patients (+20%) in each group. 36 were recruited to each group with only 1 lost to follow-up.
Selective reporting (reporting bias)	Low Risk.	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Alamoudi, 2003

Methods	Six- to eight-week prospective open study, in hospital outpatient clinics in Saudi Arabia	
Participants	**Population**: 130 patients with chronic stable asthma. (24 were excluded - 15 lost to follow-up, 9 developed exacerbation and changed dose of medication). **Baseline characteristics**: Mean age 40.2 years, with a mean duration of asthma of 11.2 years. **Inclusion criteria**: Fulfil the American Thoracic Society (1987) definition and diagnosis of asthma, chronic stable asthma, regular use of inhaled devices (pMDI or Turbohaler), incorrect inhalation technique, age >13 years. **Exclusion criteria**: Correct inhalation technique, smokers, development of an exacerbation requiring changes in doses during the 6-8 week study period, chronic obstructive airway disease.	
Interventions	Checklist used to assess inhaler technique (1-11 points for pMDI, 1-7 points for Tubohaler). The intervention was performed by a nurse with an interest in asthma education, who provided education and demonstration on correct inhaler technique, for approximately 15-20 minutes. Review at 6-8 weeks.	
Outcomes	106 patients completed the study. After education, the mean number of errors (pitfalls) reduced from 2.8±2.0 to 1.0±1.29 ($p<0.001$) for pMDI and from 0.76±1.34 to 0.081±0.28 ($p=0.002$) for Turbohaler. The improvement in inhaler technique was associated with an increase in mean PEF from 312.4±109.9 L/min to 331.0±105.8 L/min ($p=0.003$) at 6-8 weeks.	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	n/a	Pre-post test analysis, with no control group
Allocation concealment (selection bias)	n/a	None.

Blinding of participants and personnel (performance bias) All outcomes	High Risk.	All patients had the intervention.
Blinding of outcome assessment (detection bias) All outcomes	High Risk.	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	High Risk.	No sample size calculations performed.
Selective reporting (reporting bias)	Low Risk	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Ammari, 2013

Methods	Six-week parallel-grouped clinical study in English community pharmacies
Participants	**Population**: 39 adults and 17 children. 50 completed (34 adults, 16 children). **Baseline characteristics**: Mean age in adults was 40.7 years, and in children was 10.2 years. Mean FEV_1 was 93.1% predicted in adults and 93.0% predicted in children. Based on GINA 2008 guidelines, 2/39 adults had severe asthma, 6 had moderate asthma and 31 had mild asthma; 1/15 child had severe asthma, 1 had moderate asthma and 13 had mild asthma (2 could not be assessed due to lack of spirometry results). **Inclusion criteria**: Asthma, age 4 to 55 years, prescribed at least one pMDI without a spacer device. **Exclusion criteria**: Acute exacerbation of asthma or received oral prednisolone within the previous four weeks, people with other illnesses adversely affecting the respiratory system, hearing problems, or inability to distinguish between the one and two tones of the 2Tone trainer inhaler.
Interventions	The intervention was performed by the lead researcher. Measurement of peak inhalation flow (IFR) using In-Check DIAL, and assessment of pMDI inhaler technique. Patients with good inhaler technique (good co-ordination and slow IFR (<90 L/min) were placed in the control (CT) group. Patients with a fast IFR (>90 L/min) were randomised to either verbal counselling (VC) or verbal counselling plus provision of a 2Tone trainer inhaler (2T). Follow up at 6 weeks. Mini-AQLQ for adults measured at baseline and 6 weeks
Outcomes	In adults - CT, VT, 2T: Baseline Median IFR 68, 200 and 240 L/min; at 6 weeks: 88, 48.5 ($p<0.001$), 65 ($p<0.001$) L/min. Change in IFR between baseline and 6 weeks in the CT, VT and 2T groups was a median (quartiles) 12.0 L/min (–6.0, 41.0), –143.5 L/min (–176.2, –50.0; $p<0.001$), and –165.0 L/min (–225.0, –80.0; $p<0.001$) respectively. AT six-weeks, there was a significant reduction in the median (quartiles) number of incorrect steps made on an 11-point scale in both the VT (from 5.5 (5; 7) to 0 (0; 1), $p<0.01$) and 2T groups (from 5 (3; 6) to 1 (0; 2), $p<0.01$). No significant

	improvement in inhaler technique was observed in the CT group (median (quartiles) number of errors changed from 3 (1; 3.5) to 2 (1; 2.5). The mean (95% CI) change in mini-AQLQ was 0.053 (–0.41; 0.52), -0.748 (–1.37; –0.12; p<0.05), and -0.409 (–0.91; 0.09) for the CT, VT and 2T groups respectively. There was no change in lung function using FEV_1 in adults in either of the three groups, and the absence of clinically important change in quality of life may be likely to be due to the short duration of the study.	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk.	Randomisation based on a randomisation table.
Allocation concealment (selection bias)	Unclear risk.	It is not specified whether this was an open randomisation table.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk.	Allocation method unclear whether randomisation was by community pharmacy or within each pharmacy.
Blinding of outcome assessment (detection bias) All outcomes	High Risk.	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear Risk	No sample size calculations, but all patients accounted for.
Selective reporting (reporting bias)	Low Risk.	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Basheti, 2005

Methods	Two week pilot Study, in community pharmacies in Sydney, Australia.
Participants	**Population**: 26 adult asthma patients, 24 completed the study (one dropped out due to moving house, and one was unable to attend due to a leg injury) **Baseline characteristics**: Mean age 42 years. Six patients (23%) had severe asthma (based on categorisation in Asthma Management Handbook 2002, National Asthma Council Australia), 16 (62%) had moderate asthma, and 4 (15%) had mild asthma. **Inclusion criteria**: Diagnosis of asthma, dispensed a Turbohaler, aged 10 years and older. **Exclusion criteria**: patients who did not self-administer their Turbohaler, did not speak or understand English, if this was their first Turbohaler prescription.
Interventions	The intervention was performed by one of the study investigators, who is a qualified pharmacist. Turbohaler inhaler technique training by one of three methods: verbal counselling using patient information leaflet vs. augmented counselling (patient information leaflet with emphasis on essential steps) vs. augmented counselling plus

	demonstration. Review at 2 weeks.	
Outcomes	At baseline 0/26 had optimal technique. After 2 weeks, optimal technique (no minor or essential errors) achieved in 0/7, 2/8 and 7/9 in the verbal counselling, augmented counselling and augmented counselling plus demonstration groups respectively (Fisher's Exact Test for verbal counselling vs. augmented counselling plus demonstration p=0.006). The number of patients with satisfactory (some minor, but no essential errors) or optimal technique improved from 3/8 to 4/7 in the verbal counselling group, from 2/9 to 5/8 in the augmented counselling group, and from 1/9 to 9/9 in the augmented counselling plus demonstration group (verbal counselling vs. augmented counselling plus demonstration p=0.1).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk.	Computer generated list.
Allocation concealment (selection bias)	Unclear Risk.	It is not clear whether the computer generated list was sealed to conceal future allocations.
Blinding of participants and personnel (performance bias) All outcomes	High Risk.	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High Risk.	Unblinded assessments.
Incomplete outcome data (attrition bias) All outcomes	High Risk.	This was a pilot study, and so sample size calculations were not performed.
Selective reporting (reporting bias)	Low Risk.	All data reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Basheti, 2008

Methods	Six month single-blind cluster randomised parallel group study, in in community pharmacies in Sydney, Australia
Participants	**Population**: 31 community pharmacists, all trained on asthma inhaled medication and PEF technique, but only the active group (16) received education on inhaler technique and use of inhaler technique labels. 97 patients recruited (53 active, 40 control). **Baseline characteristics**: Baseline demographic data not reported. Asthma severity was classified as mild in 10%, moderate in 34% and severe in 56% of patients (using National Asthma Council Australia guidelines). **Inclusion criteria**: Age ≥14 years, with physician-diagnosed asthma, use of ICS with or without a LABA given via a Turbohaler or Accuhaler, no change in asthma medication or dose within the previous one month. **Exclusion criteria**: Patients who do not self-administer their own medicines, do not speak or understand English, were already involved in another study, or unable to complete the study follow-up.
Interventions	The intervention was performed by trained community

	pharmacists, who had attended one of three evening workshops. Inhaler technique was assessed using a 9-point checklist by a community pharmacist in the active group and a study researcher (a qualified pharmacist) in the control group. Patients in the active group received inhaler technique training using augmented counselling and demonstration, repeated up to three times until all steps were performed correctly by the patient. An inhaler technique label was stuck on the inhaler device outlining the correct steps for using the inhaler device, with incorrect steps highlighted as a reminder to the patient to remember to use their inhaler device correctly. Inhaler technique was reinforced at 1, 2, 3 and 6 months Patients in the control group received no inhaler technique education. All patients were instructed how to use a peak flow meter.	
Outcomes	The primary outcome variable for the study was peak flow variability expressed as Min%Max (lowest morning PEF as a percentage of the highest PEF over a 2-week period), however the results of this outcome measure were not reported. At 6 months, the mean inhaler technique score improved significantly from baseline in both groups, but was significantly greater for patients in the active than in the control group (for both Accuhaler and Turbohaler combined, the mean (± SD) change in score was 2.8 (±1.6) vs. 0.9 (±1.4), $p < 0.001$). In the Active group, asthma severity was significantly reduced at 2 months ($p = 0.001$), 3 months ($p < 0.001$) and 6 months ($p = 0.015$) compared with the Control group. By 3 months, only 8% of Active group patients were classified as having severe asthma compared with 22% of Control group patients ($p = 0.037$). A post hoc analysis demonstrated a significant correlation between improvement in inhaler technique score and improvement in peak flow variability ($r = 0.31$, p=0.008) and asthma-related quality of life ($r = -0.37$, p=0.001).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk.	Randomisation schedule generated using computer-generated list.
Allocation concealment (selection bias)	Unclear risk.	Allocation of pharmacies to provide either the intervention or usual care is not described, so there is an unknown selection bias.
Blinding of participants and personnel (performance bias) All outcomes	Low Risk.	Community pharmacists were blinded to the actual intervention under investigation. Pharmacists in the Active and Control groups were taught how to educate patients on correct peak flow meter technique, to provide a plausible 'sham; intervention, but only the Active group pharmacists were taught how to educate patients on correct inhaler technique.
Blinding of outcome	Low risk.	One researcher independently

assessment (detection bias) All outcomes		assessed inhaler technique of control patients, and checked for active patients
Incomplete outcome data (attrition bias) All outcomes	Low risk.	Power calculation took into account potential attrition rate and clustering effect from Pharmacies
Selective reporting (reporting bias)	High risk.	Data on the primary outcome variable of peak flow variability (Min%Max) was not reported.
Other bias	Low risk	The study appears to be free if other sources of bias.

Giraud, 2011

Methods	One month prospective observational study, in France
Participants	**Population**: 727 asthma patients at 123 community pharmacies **Baseline characteristics**: Mean age was 52 years. 61% were prescribed a pMDI, 34.5% an Autohaler and 4.5% an Easi-Breathe. **Inclusion criteria**: Up to the first 10 adult (age ≥18 years) patients at each community pharmacy, with asthma who received a prescription for an ICS in either a pDMI, Autohaler or Easi-Breathe device. **Exclusion criteria**: None specified
Interventions	The intervention was performed by community pharmacists, who had received training in the form of a 2-hour session on basic asthma treatment, inhaler technique and developing individualised instructions for each patient. All patients received the intervention of community pharmacist Inhaler technique training using verbal instruction and written instructions in the form of a sticker to attach to the inhaler device (average duration 6 minutes). Patients completed ACQ and Morsiky assessment of adherence at baseline (0 [very good adherence] to 4 [very poor adherence]), and were given a questionnaire to complete follow-up assessments (include adherence and asthma control) at 1 month and post back (completed by 503 patients (69.2%)).
Outcomes	67% of patients had previously received inhaler technique education by a healthcare professional, most commonly a respiratory physician, GP, or pharmacist. Prior to community pharmacist training, 24.1% of patients had optimal (no errors) inhaler technique, and 30% did not make any critical errors that would substantially affect dose delivery to the lungs. Immediately after community pharmacist training, optimal technique increased from 24% to 79% ($p<0.001$). Poor baseline inhaler technique was associated with worse asthma control and poor adherence (mean (SD) ACQ: 1.9 (1.2) vs. 1.4 (1.1), $p<0.001$, and mean (SD) Morisky score 1.4 (1.3) vs. 1.1 (1.2) $p<0.01$, respectively for patients with sub-optimal vs. optimal inhaler technique respectively). At 1 month, mean (SD) ACQ improved from 1.8 (1.2) to 1.4 (1.1) $p<0.001$ (n=437). There were significantly greater improvements in ACQ in patients where inhaler technique

	improved: -0.4 (0.8), compared to -0.2 (0.8) and -0.2 (0.9) in patients whose inhaler technique remained sub-optimal or remained optimal respectively, p<0.01. Self-reported adherence improved from mean (SD) 1.4 (1.3) to 1.1 (1.3), p<0.001, n=436). Similarly, there were greater improvements in adherence when inhaler technique improved (-0.4 (1.1), compared to -0.3 (1.1) and -0.1 (1.1) in patients whose inhaler technique remained sub-optimal or remained optimal respectively, p<0.001).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	n/a	There was no control group, and all patients received the intervention.
Allocation concealment (selection bias)	n/a	All patients received the intervention
Blinding of participants and personnel (performance bias) All outcomes	n/a	All patients received the intervention
Blinding of outcome assessment (detection bias) All outcomes	n/a	All patients received the intervention
Incomplete outcome data (attrition bias) All outcomes	High Risk.	No sample size calculations, and only 69.2% completed 1-month questionnaire.
Selective reporting (reporting bias)	High Risk.	Only 69.2% completed 1-month questionnaire. Furthermore ACQ and Morisky data not available for all these responding patients.
Other bias	Low risk	The study appears to be free if other sources of bias.

Appendix 3. Characteristics of included studies: The effect of interventions to improve adherence to inhaled corticosteroids on asthma control

Criteria for judging bias is based on the Cochrane handbook for systematic reviews (Higgins and Green, 2011).

Bender, 2010

Methods	Ten-week, randomised, controlled trial, in USA.	
Participants	**Population:** 50 adults; 25 in the treatment group and 25 in the control group. **Baseline characteristics:** Mean age 39.6 years in the treatment group and 43.5 years in the control group. Baseline asthma control and adherence was not reported. **Inclusion criteria:** Physician-diagnosed asthma aged 18-65 years, who were prescribed ICS. **Exclusion criteria:** Other significant medical or psychiatric disorder, or current participation in any other asthma-related clinical trial.	
Interventions	Patients were randomised to either a treatment group or control group. The intervention consisted of a 5-minute interactive voice response telephone call (repeated once or twice at 1-month intervals depending on asthma control), which comprised core educational messages, encouraged filling of ICS prescriptions and to increase communication with their physician. The control group received no telephone calls. Adherence was measured using electronic tracking device on pMDI or Accuhaler, or by weighing Turbohaler. Beliefs about medicines were measured using the BMQ - comprising 5 questions about negative medicines beliefs, and 5 questions on positive medicines beliefs (on a 1 [strongly agree] to 5 [strongly disagree]). BMQ scores from baseline and 10-week visits were calculated by subtracting the negative index total from the positive index total, so that a score >0 indicated more positive beliefs and scores <0 indicated more negative beliefs.	
Outcomes	Adherence over 10 weeks was 32% higher in the intervention arm than in the control group (mean (SD): 64.5% (17.2) vs. 49.1% (16.8), p=0.003), with a favourable shift in perception of ICS on BMQ scores (+ 0.248 (1.07) vs. -0.508 (0.913), p=0.003), which correlated with degree of adherence change (r=0.342, p=0.0152). There was no significant difference in the change in asthma control between the treatment and control groups at 10 weeks (using ACT -1.120 (3.9) vs. -1.840 (4.14) respectively; p=0.53) or quality of life (using AQLQ -0.152 (0.92) vs. -0.381 (1.06) respectively; p=0.419).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk.	Randomisation table generated before study initiation.
Allocation concealment (selection bias)	Low Risk.	Patients allocated by order of entry into study, but

		investigators remained blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low Risk.	Investigators remained blind to treatment until the final data set was completed.
Blinding of outcome assessment (detection bias) All outcomes	Low Risk.	Low Risk. Investigators remained blind to treatment until the final data set was completed.
Incomplete outcome data (attrition bias) All outcomes	Unclear Risk	Study did not describe if all patients completed study.
Selective reporting (reporting bias)	Low Risk.	All outcome measures reported.
Other bias	Low Risk	The study appears to be free if other sources of bias.

Gamble, 2011

Methods	Sequential 2 phase study, in Northern Ireland: Phase 1 was a median 9-month (range 6-12 months) observational study; Phase 2 was a 12-month prospective single blind randomised controlled trial.
Participants	**Population (Phase 1):** 239 patients. No patient had non-adherence suspected at referral to the difficult asthma clinic, however prescription analysis showed 83 were non-adherent and 156 were adherent. **Baseline characteristics (Phase 1):** Mean age of the 83 non-adherent patients was 45 years. No other information provided. **Inclusion criteria (Phase 1):** Patients referred to the regional difficult asthma service (defined at persistent symptoms of asthma despite treatment at BTS/SIGN step 4/5). **Exclusion criteria (Phase 1):** None specified. **Population (Phase 2):** 20 non-adherent patients randomised to intervention (11) or control (9). **Baseline characteristics (Phase 2):** In the intervention and control groups, mean age was 50 years and 45.2 years respectively, mean ACQ score was 3.7 and 4.0 respectively, and FEV_1 was 77.1% predicted and 78,7% predicted respectively. **Inclusion criteria (Phase 2):** Age >18 years, ACQ score >3, remaining non-adherent despite participating in Phase 1 of the study. **Exclusion criteria (Phase 2):** Current tobacco smoking, other significant co-morbidities contributing to respiratory disease.
Interventions	Phase 1: patients filling ≤50% of prescriptions were defined as non-adherent, and underwent a patient concordance consultation, resulting in an agreed treatment plan to address poor adherence. Phase 2: patients were randomised to a control group with no further intervention; or to an intervention group with an individualised psycho-educational nurse-led menu intervention to improve adherence to medication, repeated up to 8 times within a 12-week period. The Compliance Therapy Model was used to perform the intervention, encompassing the Transtheoretical Model of Change, Motivational Interviewing and Cognitive Behavioural Therapy principles.

Outcomes	Phase 1 observational study: 31 of 83 patients (37%) who were initially non-adherent significantly improved adherence after concordance interview (in these 31 patients adherence increased from 37.3% ± 14.0 to 88.5% ± 15.7 at median 9 month follow-up). This allowed a reduced ICS dose (1616.1mcg ± 490.0 vs. 1280.7mcg ± 557.6 at the 12-18 month follow-up; p<0.001), fewer rescue prednisolone courses (2.2±1.5 vs. 0.7±1.0; p<0.001) and fewer hospital admissions (p<0.006). Phase 2 study: With menu-driven intervention, adherence, in terms of percentage of prescriptions filled also improved (intervention: 37.6% to 61.9% vs. control: 31.7% to 28.8%; p=0.01). There was no significant impact on Juniper's Asthma Control Score (intervention improved from 3.7±0.7 at baseline to 2.9±1.4 at 12 months, compared to control 4.0±0.9 at baseline to 3.1±1.6 at 12 months, p=0.74). Similarly there was a lack of effect on daily ICS dose, hospital admissions, lung function, rescue course of OCS or quality of life measured using AQLQ. The lack of effect on asthma control is likely to be due to small patients numbers.

Risk of bias

Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear Risk.	Phase 2 Random sequence generation method was not described.
Allocation concealment (selection bias)	Unclear Risk.	Phase 2 allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear Risk.	Phase 2 study described as single blind, but doe not provide further details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear Risk.	Phase 2 study was not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear Risk.	Phase 2 study had no details of power calculation provided.
Selective reporting (reporting bias)	Low Risk.	No selective reporting apparent.
Other bias	Low Risk.	The study appears to be free if other sources of bias.

Garcia-Cardenas, 2013

Methods	6-month cluster randomised controlled trial, in Spain.
Participants	**Population**: 33 community pharmacies were trained to provide the intervention (29 took part in study) and 32 untrained community pharmacies were recruited for the control group (22 took part in the study). 373 patients enrolled, 346 patients completed, but one pharmacy data excluded from analysis due to lack of reliable data, therefore 336 patients were available for analysis (186 in the intervention group, 150 in the control group). **Baseline characteristics**: Mean (SD) age was 55.8 (19.1) years. Mean (SD) ACQ was 1.4 (1.1) and 1.3 (1.2) in the intervention and control groups respectively, however significantly fewer patients in the intervention group had controlled asthma (28% vs. 42.7%, p=0.005). **Inclusion criteria**: Adults aged 18 years or older with a

	physician diagnosis of asthma. **Exclusion criteria**: Participation in other asthma education programs, pregnancy, communication difficulties, suffering from seasonal asthma, or other pathologies such as COPD, lung cancer, RTIs or terminal illness.	
Interventions	Patients recruited to the intervention group received a protocol-based intervention addressing individual needs related to asthma control, inhaler technique and adherence. Patients also received education using verbal and written instructions, and physical demonstration of Turbohaler use. Patients recruited to the control group received no intervention other than their pharmacist's usual care (usually the safe supply of medicine use and advice about taking medicines). All patients in the intervention and control groups had three scheduled visits to the pharmacy, although intervention patients could have up to six visits if needed. Adherence was assessed using the 4-item Morisky-Green-Levine scale, allowing each patient to be rated as adherent or non-adherent.	
Outcomes	The proportion of patients adherent to asthma treatment increased in the intervention (from 38.2% at baseline to 60.8%, p<0.001) and control groups (from 39.3% at baseline to 55.3%, p<0.001), however the proportion of patients who were found to be adherent to treatment at 6 months was significantly higher in the intervention group than in the control group (78.5% vs. 52.0%, p < 0.001). At six months, there was a clinical and statistically significant improvement in asthma control in the intervention group (ACQ -0.66 in the intervention group (p<0.001, but not in the control group (-0.15 (p value not reported)). The mean difference between the groups in adjusted mean changes for ACQ from baseline to final visit was -0.18 (IC95% -0.37 to 0.02), p=0.079 in patients who had controlled asthma at baseline, and -0.62 (IC95% -0.80 to -0.43), p<0.001 in patients who had uncontrolled asthma at baseline. Inhaler technique improved in the intervention and control groups from baseline to 3-month intermediate visits, but only from Intermediate to final 6-month visit in the intervention group. The proportion of patients with correct inhaler technique at 6 months was significantly higher in the intervention group compared to the control group (75.8% vs. 50.0%, p < 0.001).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pharmacists /Pharmacies providing intervention or control were randomly assigned to either group, using a computer-generated list of random numbers with a 1:1 ratio of pharmacies.
Allocation concealment (selection bias)	Low risk	Allocation of pharmacies to intervention or control group performed by computer randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias)	High risk	Unblinded assessments.

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study required 342 patients assuming a 20% attrition rate. 336 completed the study, which was therefore was within acceptable limits.
Selective reporting (reporting bias)	High risk	10 patients excluded from analysis due to lack of reliable data.
Other bias	Low risk	The study appears to be free if other sources of bias.

Janson, 2009

Methods	24-week prospective randomised controlled trial, in USA.
Participants	**Population:** 95 adults, of whom 84 completed the run-in phase and were randomised in the study; 45 in the intervention group and 39 in the control group. **Baseline characteristics:** In the intervention and control groups, mean age was 36.8 years and 39.7 years respectively, measured with the validated 11-item Perceived Control of Asthma Questionnaire (PCAQ) was 16.0 and 15.8 respectively (on an 11-55 Likert scale, with low scores indicating poor perceived ability to deal with asthma and exacerbations in an effective manner). **Inclusion criteria:** Diagnosis of moderate-to-severe persistent asthma (FEV_1<80% predicted, daily symptoms, ≥1 night-time awakening per week), spirometric evidence of reversible airflow obstruction or bronchial reactivity to inhaled methacholine, and current non-smoker with ≤5 pack-years smoking history. **Exclusion criteria:** Use of systemic steroids within 4 weeks, upper respiratory tract infection within 6 weeks, pregnancy, other chronic disease, or prior participation in a formal asthma education program.
Interventions	All patients had a 4-week run-in phase, with bi-weekly visits, to stabilise fluticasone dose, then were randomised to intervention or self-monitoring. The intervention period lasted 4 weeks and comprised bi-weekly visits, followed by 14 weeks of observation, with visits held at 4-week intervals. 11 Patients withdrew during the run-in phase for reasons unspecified. 84 patients were randomised to usual care of self-monitoring alone; or to the intervention group consisting of individualised self-management education (a 30 minute intervention, comprising provision of asthma information, assessment, inhaler technique education and asthma action plan, and trigger avoidance), plus self-monitoring of symptoms and PEF, and reinforced at 2 week intervals. The intervention was performed by a practice nurse who was a certified asthma educator. No specific information about medication adherence was included in the intervention, and adherence was monitored using an electronic medication monitor attached to each patients ICS inhaler.
Outcomes	Mean ± SD adherence for the intervention and control groups was 82% vs. 80% at the end of the run-in phase, 82% vs. 77% at the end of the 4-week intervention phase, and 77% vs. 73% at the end of the study (no significant difference between groups).

	Mean change in adherence reduced in both groups over time, but was more likely to be maintained in the intervention group. The odds of maintaining a >60% adherence to ICS over the 4-week intervention period increased 9-fold in the intervention group, but was unchanged in the control group (OR 9.2 vs. 0.4, p=0.02). At the end of the 24-week study, the intervention group maintained 3-fold greater odds of >60% adherence to ICS vs. control. Over the whole study, perceived asthma control improved significantly greater in the intervention group compared to the control group (2.87 vs. 0.68, p=0.006). Quality of Life increased significantly in the intervention group (-3.82, p<0.0005), but was not significantly different in the control group (-0.80, p=0.49), and was not significantly different between the two groups (p=0.06). During the 4-week intervention period, there was a significant reduction in SABA use (incidence rate ratio 0.56, p=0.01), but this difference was maintained to the end of the study.

Risk of bias

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk.	Computer generated allocation.
Allocation concealment (selection bias)	Unclear Risk.	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low Risk.	Investigators remained blind to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low Risk.	Investigators remained blind to group assignment.
Incomplete outcome data (attrition bias) All outcomes	Low Risk.	Study required 80 patients to provide 80% power to detect a 10% change in adherence and an alpha value of 0.05. 84 patients were randomised, and ITT included all participants randomised, 78 with complete data and 6 with incomplete data.
Selective reporting (reporting bias)	Low Risk.	No selective reporting apparent.
Other bias	Low Risk.	The study appears to be free if other sources of bias.

Strandbygaard, 2010

Methods	12-week randomised prospective study, in Denmark.
Participants	**Population:** 26 patients; 12 in the intervention group and 14 in the control group. **Baseline characteristics:** Eight patients had mild persistent asthma (GINA 2), 16 had moderate persistent asthma (GINA 3) and two had severe persistent asthma (GINA 4). Nine patients were prescribed SABA alone, nine used an ICS with

	or without a LABA, and eight had not used any treatment within the past three months. **Inclusion criteria:** Diagnosis of asthma based on clinical history and daily symptoms, age 18-45 years, positive methacholine challenge test. **Exclusion criteria:** Other medical comorbidities, smoking history >10 pack-years.
Interventions	All patients were commenced on a Seretide Accuhaler at week 0. At week 4, patients randomised to receive, or to not receive, a daily SMS reminder (at 10am) on their mobile phone to take their asthma medication from weeks 4 to 12. Adherence was measured using the dose counter on the Accuhaler device.
Outcomes	At 12 weeks, the absolute difference in mean adherence rate was 17.8% (95% CI 3.2 - 32.3%), p=0.019. In the intervention group, adherence increased from 77.9% to 81.5% (mean change 3.6%, p=0.52), but decreased in the control group from 84.2% to 70.1% (mean change -14.2%, p=0.01). There was no significant difference between the two groups in terms of ACQ (mean change -0.87 [95% CI -1.4 to -0.34]; p=0.005 vs. -0.62 [95% CI -1.01 to -0.23]; p=0.005 in the intervention and control groups respectively), mini-AQLQ, exhaled nitric oxide, lung function or airway responsiveness.

Risk of bias

Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk.	Randomisation schedule performed by automatic computer generation of randomisation numbers.
Allocation concealment (selection bias)	Low Risk.	Allocation concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High Risk.	The authors did not report whether the study was open or blinded.
Blinding of outcome assessment (detection bias) All outcomes	High Risk.	The authors did not report whether the study was open or blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear Risk.	No power calculation was performed.
Selective reporting (reporting bias)	Low Risk.	All relevant outcomes reported.
Other bias	Low Risk.	The study appears to be free if other sources of bias.

Williams, 2010

Methods	12-month, cluster-randomised trial, in USA
Participants	**Population:** 193 GP practices (88 intervention, 105 control) recruited 2698 patients (1335 in the intervention group and 1363 in the control group). **Baseline characteristics:** In the intervention and control groups, mean age was 26.8 years and 28.8 years respectively, mean adherence to ICS was 25.6% and 27.7% in the three-months preceding the study. **Inclusion criteria:** Previous prescription for an ICS within the

	previous two years, age 5-56 years, continuous enrolment with GP practice for at least one year, no diagnosis of COPD or congestive heart failure. **Exclusion criteria:** If ICS was sopped before the study.	
Interventions	Patients were randomised by practice, such that individual practices were clustered as either intervention or control group practices. In the intervention group, clinicians could view updated ICS adherence information on patients via electronic prescription software. Education for medical staff on non-confrontational approaches to discussing adherence, and include ways to identify barriers to taking medication, tips to help patients remember to take their medication, and methods to promote self-efficacy. In the Control group, information on asthma on the electronic prescribing software was not available.	
Outcomes	Mean adherence over the preceding 3-months to ICS was similar at baseline in the intervention and control groups respectively (25.6% and 27.7%, p=0.21). At the end of the study mean adherence over the preceding 3-months was not statistically different (21.3% and 23.3%, p=0.553). However the intervention was not routinely performed, and adherence was significantly higher where the clinician actually viewed adherence data (35.7%) compared where the clinician did not view adherence data (12.3%, p=0.002), and in the control group (23.3%, p=0.026). All patients who had stable or improved adherence throughout study, whether in the intervention or control group, had lower rates of asthma related emergency department visits than those patients with worse adherence (aRR, 0.73 [95% CI, 0.55-0.98]; p=0.039) and there was also a lower use of OCS use (aRR, 0.77 [95% CI, 0.63-0.93]; p=0.007). However there was no significant reduction in asthma-related hospitalisations (aRR 0.77 [95% CI, 0.34-1.76]; p=0.540).	
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear Risk.	GP practices were randomly assigned as intervention or control group, but the sequence generation method was not described.
Allocation concealment (selection bias)	Unclear Risk.	Allocation of GP practices to intervention or control group was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding performed, but cluster randomisation method likely to minimise cross-contamination.
Blinding of outcome assessment (detection bias) All outcomes	Low Risk.	Outcomes ascertained by staff without knowledge of the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High Risk.	Greater than planned attrition rate. Study required a total of 2598 patients from 34 practices (i.e., 17 per arm) to have >80% power to detect a 9% absolute difference in

		adherence between study arms assuming a 2-sided a value of 0.05. 2698 patients recruited, however only 2074 patients completed the study.
Selective reporting (reporting bias)	Low Risk.	All relevant outcomes reported.
Other bias	Low Risk.	The study appears to be free if other sources of bias.

Appendix 4. Letter of support from Leeds, Bradford & Airedale, Calderdale & Kirklees Local Pharmaceutical Committees

LeedsLPC
Bradford&AiredaleLPC
Calderdale&KirkleesLPC
Working together to represent and promote community pharmacy

2 Farrar Lane
LEEDS
LS16 7AA

Tel: 0113 261 4663

Dear Sir / Madam,

Re: The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

I have had the opportunity to read the Research Proposal, and have commented and advised on the role of targeted Medicines Use Reviews as part of this study.

I believe that this study is important and is aligned with the current Local Pharmaceutical Committee's strategy of increasing interface working between hospital and community pharmacists and supports a need to increase the uptake of Medicines Use Reviews. The results of this study will be important for supporting the continued funding of this service and justifying the extended role of pharmacists.

The West Yorkshire Local Pharmaceutical Committee is supporting this study and will assist in notifying community pharmacists about the study and their role when it commences.

Yours faithfully

Robbie Turner
Chief Executive Officer
Leeds, Bradford & Airedale, Calderdale & Kirklees
Local Pharmaceutical Committees

PHARMACY
the Heart of our Community

Appendix 5. Patient invitation letter and Patient Information Sheet

Enquiries: Toby Capstick
☎ 0113 2066832
Email: Toby.Capstick@leedsth.nhs.uk

The Leeds Teaching Hospitals NHS
NHS Trust

Leeds Chest Clinic
Martin Wing
Leeds General Infirmary

Date:

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Dear

We are writing to you as you are scheduled for an appointment in the Leeds Difficult Asthma Clinic on .....

We are currently conducting a research study examining the role of pharmacists in the management of patients with difficult-to-treat-asthma, and we would like to ask you if you would be interested in participating in this study.

The treatment of asthma has traditionally been managed by doctors and more recently by specialist nurses. However we are currently exploring the role of the Pharmacist in improving asthma control, particularly in patients who like you, have difficult-to treat asthma. We are trying to learn whether pharmacists are able to improve asthma symptoms by reviewing and improving the prescribing and use of asthma medications.

As part of this study, you will be asked to perform some breathing tests and to demonstrate how you use your inhalers. You will also be asked to complete a few questionnaires to try and learn more about your experience and thoughts about the medicines you are taking for your asthma, and also about how well your asthma is controlled.

We are enclosing an information leaflet which gives you more detail about the study. Please take your time to read this information leaflet. We can discuss this study in more detail when you attend for your difficult asthma clinic appointment, where you can ask any questions about the study that you may have. You will be asked to complete a consent form before the study begins.

When you attend your clinic appointment, please bring all your medication, including your asthma inhalers with you to the clinic.

All the information we collect from this study will be treated confidentially and will not be shared with anyone outside of the asthma clinic and research team.

Thank you for your interest in assisting in this research study. If you have any questions please contact Toby Capstick, Lead Investigator for the study on **0113 2066832**.

Yours sincerely

Dr Ian Clifton
Consultant Respiratory Physician

Toby Capstick
Lead Respiratory Pharmacist
Lead Investigator

The Leeds Teaching Hospitals NHS
NHS Trust
Medicines Management & Pharmacy Services
Gledhow Wing
St James's University Hospital

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

NAMES OF INVESTIGATORS: TGD Capstick[1,2], I Clifton[1], J. Morgan[2], A.Blenkinsopp[2].
[1]Leeds Teaching Hospitals NHS Trust LS9 7TF and [2]School of Pharmacy, University of Bradford, BRADFORD, BD7 1DP

PATIENT INFORMATION SHEET

Part 1.

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. **One of our team will go through the information sheet with you and answer any questions you have**. We'd suggest this should take about 5 minutes. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?

This study is examining the benefit of a co-ordinated management strategy between a hospital Advanced Clinical Pharmacist, specialising in respiratory medicine, and community pharmacists in patients with difficult asthma.

Traditionally, the treatment of asthma has been managed by doctors and more recently by specialist nurses, who have an appropriate level of expertise to improve patients' symptoms and asthma control.

However, a number of studies have shown that a lot of patients are unable to use their inhalers adequately, or may not take their medication correctly. Consequently, this may mean that some patients do not obtain the most benefit from their treatment. The purpose of this study is to examine whether pharmacists may also be able to improve asthma symptoms by reviewing and improving the prescribing and use of asthma medications. 52 patients will be recruited to this study.

Dr Julie Morgan, who works at the School of Pharmacy in the University of Bradford and Dr Ian Clifton, who is your Consultant managing your asthma, are both supervising this study. Mr Toby Capstick, Advanced Clinical Respiratory Pharmacist will be carrying out the study.

Why have I been chosen?

You have been asked to participate in this study because you attend the Difficult Asthma Clinic. Before you take part it is important that you understand why we are doing this study and what will happen to you if you take part. Mr Capstick will use the results in a report that will be part of his Doctor of Pharmacy degree at the University of Bradford. The results will not identify any individual patients; all data will be anonymous. Please take your time to read the following information carefully and to decide whether you would like to take part.

Do I have to take part?

No, you do not have to take part.
It is up to you to decide whether to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

When you attend the Difficult Asthma Clinic, you will either receive a consultation from your doctor (usually either the Consultant or one of their team members), or from the pharmacist.

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly). What will happen to you depends on which group you are randomly assigned to.

All patients

You will be required to do the following tests at the clinic:

- Lung Function Tests. These will determine how well you can breathe in and out, and how much your breathing is obstructed by narrowing of the airways.
- Peak Inhalation Flow. This will measure how fast you breathe in when you are using your inhaler, and is useful to determine which types of inhalers you may be able to use.
- Demonstrate how you use your inhaler. This will be done with an inhaler that contains no drug, so that you do not receive any extra medication.
- Exhaled Nitric Oxide. This is another breathing test that measures asthma control.

These tests are usually performed in the difficult asthma clinic whether or not you decided to join the study. Depending on the results of your peak inhalation flow tests and how you use your inhaler, we may teach you how to use different types of inhalers or alter your asthma prescription.

You will also be required to complete some questionnaires about your asthma control and how your asthma affects you. You will also be asked about your opinions on your asthma treatment and how much you use it. If you did not join in this study, you would not be asked complete these questionnaires.

These tests and questions will be repeated six months after your first visit.
Your participation within this study will last 6 months.

Patients randomised to the Usual Care group

Participants in this group will be randomly assigned to receive an asthma consultation from your doctor (usually either the Consultant or one of their team members). You will receive a consultation with your doctor when you attend the Difficult Asthma Clinic, and again 6 months later.

Additionally, participants randomly assigned to this group will be asked not to have a 'Medicines Use Review' from their usual community pharmacist (chemist) during the 6-month study period.

Patients randomised to the Pharmacist Intervention Group
Participants in this group will be randomly assigned to receive an asthma consultation by an advanced clinical pharmacist, but your doctor will be made aware of your consultation before you leave. Each consultation with the pharmacist may take 30-60 minutes. You will receive a consultation with the pharmacist when you attend the Difficult Asthma Clinic, and again 6 months later.

If you have been randomly assigned to receive a consultation with the pharmacist in the clinic, you will also be asked to visit your usual community pharmacist (chemist) for a 'Medicines Use Review', which will take place between four and eight weeks after your first appointment at the Difficult Asthma Clinic. Your community pharmacist will book this appointment with you.

> A 'Medicines Use Review' is a medicines check - where your pharmacist will invite you to a meeting to sit down and talk about your medicines. This is to help you find out more about the medicines you are taking and pick up any problems you are having, so that your pharmacist can help them become more effective for you. This should take no more than 10 to 15 minutes, and your community pharmacist will record the consultation on paper, and share this with the investigators at the Difficult Asthma Clinic.

Expenses and payments
No expenses or payments are available for this research study.

What do I have to do?
You will be asked to attend the Difficult Asthma Clinic and complete the required tests at each visit. It is important that you keep to your scheduled visits.

If you have been randomly assigned to receive a consultation with the pharmacist in the Difficult Asthma clinic, you will also need to attend a 'Medicines Use Review' with your community pharmacist. This will be discussed further during your clinic appointment.

In between your clinic visits, you should take your asthma medication as prescribed and recommended by the Pharmacist and/or Doctor.

You should not participate in any other research studies at the same time as this study.

What is the drug, device or procedure that is being tested?
This research study is testing the benefit of a consultation with an Advanced Clinical Pharmacist in addition to a consultation with a doctor in the Difficult Asthma Clinic. There are no drugs, devices or procedures being tested in this study.

However, it is possible that your prescribed asthma medication and type of inhaler device may be altered during this study.

What are the alternatives for treatment?
If you do not take part in this study, you will receive your usual, and intended, consultation with the doctor in the Difficult Asthma Clinic. You will not receive a consultation with the Pharmacist.

What are the possible disadvantages and risks of taking part?

Your asthma medication and the type of inhaler prescribed may be changed during this study in order to improve your asthma symptoms. The side effects of any new medications will be explained to you before they are prescribed. However your new medications are likely to be similar to those you are currently taking and serious side effects are not expected. Changes to your medication may take place even if you are not participating in this study.

What are the possible benefits of taking part?

We cannot promise that this study will help you, but doing the study may improve the way you're are able to use your inhalers and so may improve the control of your asthma.

It is also possible that the information that we get from this study may help improve the treatment of other people with asthma.

What happens when the research study stops?

At the end of the study, if you continue to need to attend the Difficult Asthma Clinic, you will only receive a consultation with the Doctor.

What if there is a problem?

This study has been carefully reviewed and we hope that there will not be any problems. However, if you have any complaint about the way you have been dealt with during the study or believe that you have suffered any possible harm, please let us know and this will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2.

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the method of treatment that is being studied. If this happens, your research pharmacist will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research pharmacist will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an agreement outlining the discussion.

Also, on receiving new information your research pharmacist might consider it to be in your best interests to withdraw you from the study. He will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time but information collected may still be used. If you continue to need to attend the Difficult Asthma Clinic, you will only receive a consultation with the Doctor.

What if there is a problem?
If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions (contact Mr Toby Capstick, Tel: 0113 2066832). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the unlikely event of something going wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leeds Teaching Hospitals NHS Trust. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?
We will record information about your asthma treatment throughout this study, and we will obtain prescription records from your GP and regular Community Pharmacist (chemist), as well as a copy of any record of Medicines Use Review performed by your Community Pharmacist. This information will be collected by the research pharmacist. All information that is collected about you during the course of the research will be kept strictly confidential. This information will be stored in a secure area of the hospital. We will destroy all identifiable information five years after the end of this study.

By signing the Study Consent Form, you will be agreeing that the study monitors, the Leeds Teaching Hospitals NHS Trust Ethics Committee, study sponsor and regulatory agencies, will be granted direct access to your medical notes for verification of the study procedures and dates of study, without violating the confidentiality of your medical records. This access may also be required if you agree to participate in this study, and later withdraw.

Involvement of the General Practitioner / Family doctor (GP)
We will inform your GP, as well as your regular Community Pharmacist that you have taken part in this study.

Your GP will be informed of any changes to your asthma medication made during the course of the study, and your progress. This information would normally be provided to your GP after you have attended the Difficult Asthma Clinic, even if you did not participate in this research study.

What will happen to the results of the research study?
We will publish the results in a scientific journal and/or at a conference. You will not be personally identified in any publication we produce.

Who is organising and funding the research?
This is a combined study between the Leeds Teaching Hospitals NHS Trust and the University of Bradford, with no commercial sponsorship.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Humber Bridge Research Ethics Committee.

Further Information and Contact Details
For further information regarding this study, please contact Mr Toby Capstick, Tel: 0113 2066832.

If you would like to speak to someone who is not involved with this study, the Patient Advice and Liaison Service (PALS) may be able to help. There are also 'Comment Boxes' around the hospitals to enable you to "have your say", whether this is good or not so good!

Appendix 6. Patient Consent Forms

(PI and UC groups)

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Name: .....
Date of Birth: .....
Hospital Number: .....
Study Number: .....

Medicines Management &Pharmacy Services
Gledhow Wing

PATIENT CONSENT FORM

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Names of Researchers: TGD Capstick, I Clifton, J. Morgan, A. Blenkinsopp.

Please initial box

1. I confirm that I have read and understood the information sheet dated 28th June 2012 (Version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Bradford, from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I agree to my Community Pharmacist being informed of my participation in the study, and for information from any Medicines Use Review being shared with research team. ☐
6. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

Consent Form PI Group. Version 4 Date: 23rd July 2012
When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

The Leeds Teaching Hospitals NHS
NHS Trust

Patient Name: .....
Date of Birth: .....
Hospital Number: .....
Study Number: .....

Medicines Management &Pharmacy Services
Gledhow Wing

PATIENT CONSENT FORM

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Names of Researchers: TGD Capstick, I Clifton, J. Morgan, A. Blenkinsopp.

Please initial box

1. I confirm that I have read and understood the information sheet dated 28th June 2012 (Version 4) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Bradford, from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I agree to my Community Pharmacist being informed of my participation in the study. ☐
6. I agree not to have a Medicines Use Review during the 6 month study period. However if a Medicines Use Review does take place, I agree that the information may be shared with research team. ☐
7. I agree to take part in the above study ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

Consent Form UC Group. Version 4 Date: 23rd July 2012

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.

Appendix 7. Asthma Clinic Format – PI Group

DPharm Project
Asthma Clinic - Format

Patient Recruitment

Time	Action	Comments
-2 weeks	1. Review Clinic list for 2 weeks time: 2. Identify suitable patients with Ian Clifton 3. Post study invitation letter to patient	1. Ensure clinic secretaries provide list 2. Will notes be available? 3. Ensure LTHT post is efficient
0 weeks	1. Discuss study with patient a. Accept: recruit – enter study & randomise b. Decline: enter usual clinic pathway 2. Study interventions and data collection 3. Patients in intervention arm – refer to community pharmacy for t-MUR	1. Check meet all inclusion criteria 2. Discuss with clinic nurses re: data collection
4-8 weeks	1. t-MUR with community pharmacy 2. Community pharmacy provides copy of MUR data form.	1. As per usual NHS service; plus objective inhaler assessment using checklists 2. Study to provide SAE
6 months	1. Final visit in study 2. Data collection	1. Explain end of study, but usual treatment continues under NHS

Study Format

1. **Recruitment**
   - When patient arrives in clinic:
     - Immediately enters pharmacist room to discuss study – study format, questionnaires & investigations etc, purpose etc.
   - If patient agrees to participate in the study, proceed as follows:
     - Principal Investigator checks patient meets all inclusion criteria (using **Patient CRF: Section 1**)
     - Principal Investigator obtains written informed consent

2. **Randomisation**
   - Principal Investigator randomises patient into study – into either the Pharmacist Intervention (PI) or Usual Care (UC) group, and documents on **Randomisation Log** and **Patient CRF**

3. **Baseline Questions for ALL Patients**
   - Principal Investigator completes Baseline Demographic Data (**Patient CRF: Section 2**)
   - Baseline data on Medical / Social History, will be completed by Principal Investigator for PI group and by the clinic Doctor for the UC group (**Patient CRF: Section 2**)

4. **Patient Self-Completed Questionnaires**
   - Each patient, whether randomising to the PI or UC group, will be asked to complete the following questionnaires in a separate quiet room.
     - ACQ
     - AQLQ(S)
     - EQ-5D-5L
     - MARS
     - BMQ
   - After completing each question, the Principal Investigator or nurse must check that all questions have been completed.
   - Completion of these questions should be confirmed on the CRF (**Patient CRF: Section 5 and 7**)

5. **Inhaler Devices and Inspiratory Flow**
   - Patient's ability to use inhaler devices and preference for different inhalers will be assessed by the Principal Investigator for PI group and by the clinic Nurse for the UC group (**Patient CRF: Section 6**):
     - Peak Expiratory Flow: Correct technique, and whether the patient has one that they use.
     - Whether the patient has previously been taught how to use their current inhaler devices.
     - Inspiratory Flow before and after instruction
     - Inhaler Technique before and after instruction
     - Patient Preference for different devices

6. **Clinic Review**
   - UC group receives review and assessment by their clinic Doctor (Consultant or Specialist Registrar):
     - Where appropriate: past medical history, social history, family history.
     - Assessment of asthma control
     - Adherence assessment
     - Inhaler technique
     - Review of aggravating factors
     - Treatment is stepped up or stepped down as appropriate
   - PI group receives review and assessment by the Pharmacist (Principal Investigator) [see below]:
     - Assessment of asthma control
     - Adherence assessment
     - Inhaler technique
     - Review of aggravating factors
     - Treatment is stepped up or stepped down as appropriate
   - Documentation required for study:
     - Medical /Social History (**Patient CRF: Section 2**)
     - Duration of clinic visit – including time taken by nurse to complete inhaler technique assessments, but NOT completion of questionnaires (**Patient CRF: Section 3**)
     - Current medication (**Patient CRF: Section 4**)
     - Asthma Outcome data – exacerbations in the past 4 weeks, lung function, smoking status and current use of an Asthma Action Plan (**Patient CRF: Section 5**)
     - Recommended changes in treatment regimen (**Patient CRF: Section 8**)

7. **Referral for targeted Medicines Use Review (t-MUR)**
   - UC group: Should be advised NOT to have a t-MUR during the study period.
   - PI group: The Principal Investigator will refer the patient for a t-MUR at the patient's usual community pharmacy in 6-8 weeks.

8. **Follow Up**
   - All patients will be reappointed for another visit at the Leeds Difficult Asthma Clinic 24 weeks (6 months) after their baseline visit.

9. **Six-month Visit**
   - Steps 4 to 6 will be repeated

Format of Clinic Review by Pharmacist (Principal Investigator)

1. **General Review**
   - Where appropriate:
     - Past asthma history (e.g. exacerbation frequency, number of hospital and ICU admissions, use of corticosteroid rescue courses, symptoms experienced during exacerbations).
     - Linked medical conditions e.g. symptoms of GORD, rhinitis.
     - Social history (e.g. smoking history and alcohol consumption, housing condition [e.g. presence of mould or damp, pets, dust etc).
     - Family history

2. **Assessment of asthma control**
   - Use information from ACQ, AQLQ(S), EQ-5D-5L.
   - RCP 3 Questions: Yes/no or graded response to the following three questions. In the last week (or month)
     1. Have you had difficulty sleeping because of your asthma symptoms (including cough)?
     2. Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?
     3. Has your asthma interfered with your usual activities (e.g. housework, work/ school etc)?
   - Lung Function (Peak Flow, FEV_1, FEV_1/FVC, FeNO)
   - Exacerbations (steroid courses, A&E attendances / Hospitalisations in the past 4 weeks)
   - Check frequency of use of SABA

3. **Adherence assessment**
   - Use information from the MARS and BMQ
   - Ask patient about adherence

4. **Inhaler technique**
   - Use checklists

5. **Review of aggravating factors**
   - Allergies
   - Lifestyle (where appropriate: diet & nutrition, smoking, physical activity, alcohol, sexual health, weight management etc)
   - Factors that trigger exacerbations and deterioration in asthma control (e.g./ dust, pollen, pets etc).

6. **Education**
   - Asthma – condition, pathology
   - Role of drug therapy:
     - Why they are used / what they are for
     - When / how to take their medicines
     - Side effects and how to manage them
   - Monitoring, Asthma Action Plan, Self Management

7. **Signposting**
   - Vaccines
   - Patient Information leaflets
   - Self-help groups (e.g. Breathe Easy, Asthma UK).

8. **Treatment is stepped up or stepped down as appropriate**
   - Review of current treatment regimen
   - Optimisation and rationalisation of the therapy.

Appendix 8. Inhaler Technique Assessment Checklists

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No……. Date……

Inhaler Technique Assessment

The above patient, who usually uses your community pharmacy, has been enrolled into a clinical study currently being conducted at the Leeds Teaching Hospitals in conjunction with the University of Bradford.

Patients randomised to the Pharmacist Intervention arm of the study should have a Targeted MUR from their usual community pharmacist within 6 to 8 weeks of recruitment. Inhaler technique assessment and training should form one aspect of an asthma MUR. We would be grateful if the enclosed Inhaler Technique Checklists could be used to assess this patient's inhaler technique.

This will allow the study investigators to assess how well patients are able to use their inhaler device after an initial assessment and training of inhaler technique at the start of the study (4 to 8 weeks prior to their Targeted MUR), and then again at 6 months

Instructions for Use

1. Complete checklists for all inhaler devices that the patient is currently using.
2. Ask the patient to demonstrate inhaler technique with their usual inhalers using the appropriate checklist.
3. Record a tick for each step completed correctly, and a cross if not performed correctly, in the 'Before Instruction' column.
4. If inhaler technique is not perfect (all steps performed correctly), please explain which steps were not performed correctly, and if possible demonstrate correct inhaler technique using a placebo inhaler.
5. Recheck the patient's inhaler technique.
6. Record a tick for each step completed correctly, and a cross if not performed correctly, in the 'After Instruction' column.
7. Repeat re-education and recheck technique up to a maximum of three times until perfect technique achieved.
8. NB. If inhaler technique is perfect (all steps performed correctly) when the patient first demonstrates their technique, it does not need to be repeated.
9. The total score and percentage will be calculated by the Study Lead Investigator
10. Once completed, please return the forms to:

    Toby Capstick,
    Pharmacy Department,
    St. James's University Hospital
    Leeds
    LS9 7TF

NB. This will not look at rinsing mouth after using steroid inhalers - i.e. it only looks at the steps taken that are common to all drugs in the same device. Nor does this assess the initial loading and priming of the device(s) where appropriate (e.g. for the Respimat device, assume that the canister has been loaded into the inhaler and the device primed).

1

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

1. MDI

Step Number	Checklist	Before Instruction	After Instruction
1	Remove Cap / mouthpiece cover		
2	Check inside and outside of inhaler, including mouthpiece for presence of loose objects		
3	Shake inhaler well		
4	Hold inhaler upright between fingers and thumb, with thumb on the base		
5	Exhale to residual volume		
6	Exhale away from mouthpiece		
7	Place mouthpiece between teeth and lips		
8	Breathe in slowly and deeply through the mouth		
9	Actuate dose just after starting to breath in		
10	Hold breath for 10 seconds or as long is as comfortable		
11	Replace cap / mouthpiece cover		
	TOTAL		
	PERCENTAGE		

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Brennan VK, Osman LM, Graham H *et al.* True device compliance: the need to consider both competence and contrivance. *Respir Med* 2005;99:97-102.
3. Cochrane MG, Bala MV, Downs KE *et al.* Inhaled Corticosteroids for Asthma Therapy* Patient Compliance, Devices, and Inhalation Technique. *Chest* 2000; 117:542-550
4. Dahl R, Becker V, Oligaard B *et al.* Assessment of patient preference of the handihaler compared with the metered dose inhaler four weeks after instruction. *Respiratory Medicine* 2003;97:1126-33.
5. Erickson SR, Landino HM, Zarowitz BJ *et* Kirki DM. Pharmacists' understanding of patient education on metered-dose inhaler technique *The Annals of Pharmacotherapy* 2000;34, No. 11, pp. 1249-1256
6. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html
7. Hanania NA, Wittman R, Kesten S et al. Medical personnel's knowledge of and ability to use inhaling devices: metered-dose inhalers, spacing chambers and breath-actuated dry powder inhalers. Chest 1994;105:111-7.
8. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices *Respiratory Medicine* 2000:94 496-500
9. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/ [Seretide, Alvesco, Pulmicort]
10. Thompson J, Irvine T, Grathwohl K et Roth B. Misuse of metered-dose inhalers in hospitalized patients *Chest* 1994;105:715-717

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name..... Study No..... Date.....

2. Accuhaler

Step Number	Checklist	Before Instruction	After Instruction
1	Open inhaler		
2	Push lever back completely		
3	Exhale to residual volume		
4	Exhale away from mouthpiece		
5	Mouthpiece between teeth and lips		
6	Inhale forcefully and deeply		
7	Hold breath for 10 seconds		
8	Exhale away from mouthpiece		
9	Close inhaler		
	TOTAL		
	PERCENTAGE		

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Basheti IA, Armour CL, Bosnic-Anticevich SZ *et al.* Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Patient Education and Counselling* 2008;72:26-33.
3. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html
4. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices *Respiratory Medicine* 2000:94 496-500
5. Rönmark E, Jögi R, Lindqvist A *et al.* Correct use of three powder inhalers: comparison between diskus, turbuhaler, and easyhaler. *J Asthma* 2005;42:173-8.
6. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/ [Seretide]
7. van der Palen J, Klein JJ, Schildkamp AM. Comparison of a new multi-dose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma* 1998;35:147-52.

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

3. Turbohaler

Step Number	Checklist	Before Instruction	After Instruction
1	Remove the cap from the inhaler		
2	Keep inhaler upright		
3	Rotate grip forwards then backwards until a click is heard (it does not matter which way the grip is turned first)		
4	Exhale to residual volume		
5	Exhale away from mouthpiece		
6	Place mouthpiece between teeth and lips		
7	Inhale forcefully and deeply		
8	Hold breathe for 10 seconds or as long is as comfortable (NB SPC & Asthma UK don't specify to hold breath!; duration from GINA/NARTC)		
9	Exhale away from mouthpiece		
10	Replace cap		
	TOTAL		
	PERCENTAGE		

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Basheti IA, Armour CL, Bosnic-Anticevich SZ *et al.* Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Patient Education and Counselling* 2008;72:26-33.
3. Basheti IA, Reddel HK, Armour CL *et al.* Counseling about turbuhaler technique: needs assessment and effective strategies for community pharmacists. *Respiratory Care* 2005;50:617-23.
4. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html
5. Hanania NA, Wittman R, Kesten S et al. Medical personnel's knowledge of and ability to use inhaling devices: metered-dose inhalers, spacing chambers and breath-actuated dry powder inhalers. Chest 1994;105:111-7.
6. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices *Respiratory Medicine* 2000:94 496-500
7. Rönmark E, Jögi R, Lindqvist A *et al.* Correct use of three powder inhalers: comparison between diskus, turbuhaler, and easyhaler. *J Asthma* 2005;42:173-8.
8. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/ [Seretide, Pulmicort, Bricanyl]
9. van der Palen J, Klein JJ, Schildkamp AM. Comparison of a new multi-dose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma* 1998;35:147-52.

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

4. Easi-Breathe

Step Number	Checklist	Before Instruction	After Instruction
1	Shake inhaler		
2	Keep inhaler upright, do not block air holes at the top		
3	Open cap		
4	Exhale to residual volume		
5	Exhale away from the mouthpiece		
6	Place mouthpiece between teeth and lips		
7	Inhale slowly and deeply. Do not stop breathing when the inhaler 'puffs'		
8	Hold breath for 10 seconds or as long is comfortable		
9	Close cap		
	TOTAL		
	PERCENTAGE		

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html
3. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices *Respiratory Medicine* 2000:94 496-500

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

5. Easyhaler

Step Number	Checklist	Before Instruction	After Instruction
1	Remove Cap / mouthpiece cover		
2	Shake inhaler well		
3	Hold inhaler upright		
4	Exhale to residual volume		
5	Exhale away from mouthpiece		
6	Actuate dose prior to inhalation		
7	Place mouthpiece between teeth and lips		
8	Inhale forcefully and deeply		
9	Hold breathe for 5 to 10 seconds or as long is as comfortable		
10	Replace cap		
	TOTAL		
	PERCENTAGE		

References

1. Rönmark E, Jögi R, Lindqvist A *et al*. Correct use of three powder inhalers: comparison between diskus, turbuhaler, and easyhaler. *J Asthma* 2005;42:173-8.
2. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/ [Easyhaler]

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name..... Study No..... Date.....

6. HandiHaler

Step Number	Checklist	Before Instruction	After Instruction
1	Open dust cap		
2	Open mouthpiece		
3	Remove capsule from blister strip		
4	Insert capsule into centre chamber		
5	Close mouthpiece until click heard		
6	Keep inhaler upright and press the piercing button once and release		
7	Exhale to residual volume		
8	Exhale away from the mouthpiece		
9	Place mouthpiece between teeth and lips		
10	Inhale slowly and deeply, but at a rate sufficient to hear the capsule vibrate		
11	Repeat steps 7-10 in order to empty the capsule completely		
12	Open mouthpiece to empty the used capsule		
13	Close the mouthpiece and dust cap		
	TOTAL		
	PERCENTAGE		

References

1. Dahl R, Becker V, Oligaard B *et al.* Assessment of patient preference of the handihaler compared with the metered dose inhaler four weeks after instruction. *Respiratory Medicine* 2003;97:1126-33.
2. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/ [Spiriva]

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

7. Respimat (assume already loaded and prepared for use)

Step Number	Checklist	Before Instruction	After Instruction
1	Keep inhaler upright		
2	Turn the base in the direction of the red arrows until it clicks		
3	Open cap		
4	Exhale to residual volume		
5	Exhale away from the mouthpiece		
6	Place mouthpiece horizontally between the teeth and lips, without covering the air vents		
7	Breathe in slowly and deeply through the mouth		
8	Actuate dose just after starting to breath in		
9	Hold breathe for 10 seconds or as long is as comfortable		
10	Close cap		
	TOTAL		
	PERCENTAGE		

References

1. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/ [Spiriva]

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

8. MDI plus Spacer (multiple breath technique)

Step Number	Checklist	Before Instruction	After Instruction
1	Assemble the two parts of the volumatic spacer		
2	Remove Cap / mouthpiece cover from inhaler		
3	Check inside and outside of inhaler, including mouthpiece for presence of loose objects		
4	Shake inhaler well		
5	Place mouthpiece of inhaler into flat end of the volumatic spacer		
6	Hold inhaler upright between fingers and thumb, with thumb on the base		
7	Exhale to residual volume		
8	Exhale away from mouthpiece		
9	Place mouthpiece of volumatic spacer between teeth and lips		
10	Actuate one dose into volumatic spacer		
11	Breathe in slowly and deeply through the mouth into the volumatic spacer.		
12	Breathe into and out of the volumatic spacer 5 to 6 times.		
13	Remove inhaler from volumatic spacer		
14	Replace cap / mouthpiece cover on inhaler		
	TOTAL		
	PERCENTAGE		

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Brennan VK, Osman LM, Graham H *et al.* True device compliance: the need to consider both competence and contrivance. *Respir Med* 2005;99:97-102.
3. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name…… Study No…… Date……

9. MDI plus Spacer (single breath technique)

Step Number	Checklist	Before Instruction	After Instruction
1	Remove cap from aerochamber		
2	Remove cap / mouthpiece cover from inhaler		
3	Check inside and outside of inhaler, including mouthpiece for presence of loose objects		
4	Shake inhaler well		
5	Place mouthpiece of inhaler into flat end of the aerochamber		
6	Hold inhaler upright between fingers and thumb, with thumb on the base		
7	Exhale to residual volume		
8	Exhale away from mouthpiece		
9	Place mouthpiece of aerochamber between teeth and lips		
10	Actuate one dose into aerochamber		
11	Breathe in **slowly** and deeply through the mouth into the aerochamber. (If a whistling sound is heard, the inspiratory rate is too fast)		
12	Hold breathe for 10 seconds or as long is as comfortable		
13	Remove inhaler from aerochamber		
14	Replace cap / mouthpiece cover		
	TOTAL		
	PERCENTAGE		

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Brennan VK, Osman LM, Graham H *et al.* True device compliance: the need to consider both competence and contrivance. *Respir Med* 2005;99:97-102.
3. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html
4. Hanania NA, Wittman R, Kesten S et al. Medical personnel's knowledge of and ability to use inhaling devices: metered-dose inhalers, spacing chambers and breath-actuated dry powder inhalers. Chest 1994;105:111-7.
5. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices *Respiratory Medicine* 2000:94 496-500
6. Thompson J, Irvine T, Grathwohl K et Roth B. Misuse of metered-dose inhalers in hospitalized patients *Chest* 1994;105:715-717

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Inhaler Technique Checklists

Patient Name..... Study No..... Date.....

References

1. Asthma UK. Using your inhalers. Last updated 19th April 2012. Available at: http://www.asthma.org.uk/about-asthma/medicines-treatments/using-your-inhalers/
2. Basheti IA, Armour CL, Bosnic-Anticevich SZ *et al*. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Patient Education and Counselling* 2008;72:26-33.
3. Basheti IA, Reddel HK, Armour CL *et al*. Counseling about turbuhaler technique: needs assessment and effective strategies for community pharmacists. *Respiratory Care* 2005;50:617-23.
4. Brennan VK, Osman LM, Graham H *et al*. True device compliance: the need to consider both competence and contrivance. *Respir Med* 2005;99:97-102.
5. Cochrane MG, Bala MV, Downs KE *et al*. Inhaled Corticosteroids for Asthma Therapy* Patient Compliance, Devices, and Inhalation Technique. *Chest* 2000; 117:542-550
6. Dahl R, Backer V, Ollgaard B *et al*. Assessment of patient preference of the handihaler compared with the metered dose inhaler four weeks after instruction. *Respiratory Medicine* 2003;97:1126-33.
7. Erickson SR, Landino HM, Zarowitz BJ *et* Kirki DM. Pharmacists' understanding of patient education on metered-dose inhaler technique *The Annals of Pharmacotherapy* 2000;34, No. 11, pp. 1249-1256
8. Global Initiative for Asthma / National Asthma and Respiratory Training Centre. Instructions for Inhaler and Spacer Use. Available at: http://www.ginasthma.org/other-resources-instructions-for-inhaler-and-spacer-use.html
9. Hanania NA, Wittman R, Kesten S et al. Medical personnel's knowledge of and ability to use inhaling devices: metered-dose inhalers, spacing chambers and breath-actuated dry powder inhalers. Chest 1994;105:111-7.
10. Lenney J, Innes JA, Crompton GK. Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices *Respiratory Medicine* 2000:94 496-500
11. Rönmark E, Jögi R, Lindqvist A *et al*. Correct use of three powder inhalers: comparison between diskus, turbuhaler, and easyhaler. *J Asthma* 2005;42:173-8.
12. Summary of Product Characteristics. Electronic Medicines Compendium. Datapharm Communications Ltd. http://emc.medicines.org.uk/
13. Thompson J, Irvine T, Grathwohl K et Roth B. Misuse of metered-dose inhalers in hospitalized patients *Chest* 1994;105:715-717
14. van der Palen J, Jlein JJ, Schildkamp AM. Comparison of a new multi-dose powder inhaler (Diskus/Accuhaler) and the Turbuhaler regarding preference and ease of use. *J Asthma* 1998;35:147-52.

Appendix 9. Targeted Medicines Use Review Referral Form

Community Pharmacy Request Form NHS

RESEARCH STUDY

The Effectiveness of Pharmacist Interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma

Targeted Medicine Use Review

Name of patient:		Date of birth:	
Address of patient:			
Patient's contact telephone number:			
GP:		Community Pharmacy:	

Patient: □	will contact pharmacy to arrange an appointment
□	requests that pharmacy contacts patient to make an appointment

This patient has been recruited to the above study and requires:

Targeted Medicines Use Review (t-MUR)
This should be performed between 4 and 8 weeks of the date of this request form.

Comments (state specific issues and possible goals):

Hospital Pharmacy

□	Patient has consented to information about their medication being supplied to their nominated pharmacy.
□	The community pharmacy has been contacted by telephone to discuss this service request.

Name of person referring:	Toby Capstick		
Address	Pharmacy Dept, St James's University Hospital, Beckett Street, Leeds, LS9 7TF		
Position	Lead Respiratory Pharmacist / Lead Study Investigator		
Contact number:	0113 2066832	Date:	

Community Pharmacy

Pharmacist name:			
Date patient contacted:		Date service completed:	

Community Pharmacy:
Retain this completed form for monitoring purposes.
Please post a copy of the completed MUR form to the research team in the stamped addressed envelope provided

Appendix 10. Patient Case Record Form

I. Patient Case Record Form

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

1. Study Inclusion Criteria

PI: TC UC: TC

Inclusion Criteria	Yes	No
1. Clinical diagnosis of asthma		
2. Fulfils criteria for difficult asthma (defined as persistent symptoms and/or frequent exacerbations despite treatment at step 4 or step 5 of the BTS 2011 guidelines)		
3. Administers their own medications independently		
4. Age between 18 and 70 years		
5. Able to speak, read and write in English		
6. Available for full 6 month follow up period		
7. Patient agrees to MUR from their usual community pharmacy		
8. Patient's usual community pharmacy undertakes and is registered with Leeds PCT to undertake MURs		
9. Patient has not had a MUR within the past 12 months		
10. Patient receives their regular medication from the same Community Pharmacy for at least 3 months prior to their baseline visit		
11. Provide written informed consent		

- Patient may enter the study if all criteria are ticked as 'Yes'
- If any criteria are ticked as 'No' then the patient must not enrol in the study

2. Baseline Data

Demographic Data

PI: TC UC: TC

Patient Initials		Date of Study Entry	
Date of Birth		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC
Sex	Male / Female	Date Consent Obtained	
MUR Referral Sent [PI only]	(date)	MUR Documentation Received	

Medical / Social History

PI: TC UC: Dr

Occupation		No. of Steroid courses in past 12 months	
Period of asthma instability		No. A&E attendances / hospitalisations in past 12 months	
Beclometasone equivalent dose			

3. Duration of Clinic Visit

PI: TC UC: Dr

	0 Months	6 Months
Time Spent in Clinic		

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

4. Medication

PI: TC UC: Dr

Class of Drug	Generic Name	Strength	Device	Dose	Date started	Date stopped
ICS						
LABA						
ICS/LABA						
SABA						
LKTa						
Methylxanthine						
Anti-IgE						
LAMA						

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

5. Asthma Outcome Data

PI & UC: Patient (TC / Nurse to check fully completed)

Asthma Control: Juniper's ACQ

See separate Sheet

	0 Months	6 Months
ACQ Performed (tick box)		

Asthma Quality of Life: Juniper's AQLQ(S)

See separate Sheet

	0 Months	6 Months
AQLQ(S) Performed (tick box)		

Asthma Quality of Life: EQ-5Q-5D

See separate Sheet

	0 Months	6 Months
EQ-5D-5L Performed (tick box)		

PI: TC UC: Dr

Visit	0 Months	6 Months
Date		
No. oral steroid courses in past 3 months		
No. A&E attendances / hospitalisations in past 3 months		
FEV_1		
FEV_1/FVC		
FeNO		
Current Smoking Status		
Does patient have Action Plan?		
Current ICS (beclometasone equivalent) Dose		
Frequency of use of SABA		

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

6. Inhaler Devices and Inspiratory Flow

PI: TC UC: Nurse

Visit	0 Months	6 Months
Date		
Does patient have PEF meter + diary?		
Can patient use PEF meter?		
Comments		

PI: TC UC: Nurse

Previous Inhaler Teaching	
Has patient previously received had their inhaler technique checked (yes/no)	
Inhaler technique checked by whom? (e.g. Dr, nurse, pharmacist)	
Comments	

PI: TC UC: Nurse

Inspiratory Flow *Before* and *After* Instruction

Device	Clinically Effective Inspiratory Flow	Visit					
		0 Months		4-8 weeks (t-MUR)*		6 Months	
		Before	After	Before	Before	After	Before
pMDI	25-60 L/min						
Accuhaler	30-90 L/min						
Turbohaler	30-90 L/min						
HandiHaler	20-60 L/min						
Easi-Breathe	20-60 L/min						
Easyhaler							

*NB. Inspiratory Flow may not be performed by Community Pharmacy as part of t-MUR, and many may not have In Check DIAL Inspiratory Flow Meters

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

PI: TC UC: Nurse

Inhaler Technique *Before* and *After* Instruction				
Device	Criteria	Visit		
		0 Months	4-8 weeks (t-MUR)	6 Months
pMDI	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
Accuhaler	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
Turbohaler	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
HandiHaler	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
Easi-Breathe	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
Easyhaler	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			
	Percentage score before instruction			
	Percentage score after instruction			
	No. of times instruction had to be repeated			

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

PI: TC UC: Nurse

Patient Preference of Inhaler Device		
Rank	Visit	
	0 Months	6 Months
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

7. Medication Beliefs and Adherence

PI & UC: Patient

Beliefs about Medicines Questionnaire

See separate Sheet

	0 Months	6 Months
BMQ Performed (tick box)		

Adherence:

a. Patient reported adherence (MARS)

See separate Sheet

	0 Months	6 Months
MARS Performed (tick box)		

PI & UC: TC

b. GP & Community Pharmacy reported adherence (number of prescriptions written)

See separate Sheets

	0 Months	6 Months
GP Contacted (tick box)		
GP Info Received (tick box)		
Pharmacy Contacted (tick box)		
Pharmacy Info Received (tick box)		

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

8. Medication Adjustment

PI: TC UC: Doctor

Medication Adjustments			
Reason for Rx change	Visit		
	0 Months	4-8 weeks (t-MUR)	6 Months
Due to switching device			
Attempt to optimise control			
Inappropriate treatment (e.g. duplication)			
Other			

Details	
0 Months	
4-8 weeks (t-MUR)	
6 Months	

9. Targeted Medicines Use Review (t-MUR)

PI: TC UC: n/a

Treatment Arm	PI / UC
Community Pharmacy Details	
Date Patient Referred for t-MUR	
Date of t-MUR	
Date t-MUR Form Received	
Action from t-MUR	

II. Patient Feedback from t-MUR

Patient Case Record Form

Patient Initials		Patient Study Number	
Hospital No.		Treatment Arm	PI / UC

1. Targeted Medicines Use Review

Date	

1.1. Pharmacist Intervention (PI) Group

Proposed Question:
Tell me about how the MUR went with your Community Pharmacy?

Did patient have t-MUR?	Yes / No

	Comments
If had t-MUR:	

	Comments
If did not have MUR:	

1.2. Usual Care (UC) Group

Proposed Question:
Tell me about how the MUR went with your Community Pharmacy?

Did patient have t-MUR?	Yes / No

	Comments
If had t-MUR:	

	Comments
If did not have MUR:	

MUR Feedback – Additional Page

III. Asthma Control Questionnaire (ACQ)

ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR THE UK)

PATIENT ID:_____

DATE:_____

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

ASTHMA CONTROL QUESTIONNAIRE©
(ENGLISH FOR THE UK)

PATIENT ID:_____

DATE:_____

5.	In general, during the past week, how much time did you **wheeze?**	0 Never 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6.	On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0 None 1 1 - 2 puffs/inhalations most days 2 3 - 4 puffs/inhalations most days 3 5 - 8 puffs/inhalations most days 4 9 - 12 puffs/inhalations most days 5 13 - 16 puffs/inhalations most days 6 More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7.	FEV_1pre-bronchodilator: ..... FEV_1predicted:..... FEV_1%predicted:..... (Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	0 > 95% predicted 1 95 - 90% 2 89 - 80% 3 79 - 70% 4 69 - 60% 5 59 - 50% 6 < 50% predicted

IV. Standardised Asthma Quality of Life Questionnaire (AQLQ(S))

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____
(UNITED KINGDOM)
SELF-ADMINISTERED DATE _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____
(UNITED KINGDOM)
SELF-ADMINISTERED DATE _____

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Most Not Done		Several Not Done		Very Few Not Done		No Limitation
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____
(UNITED KINGDOM)
SELF-ADMINISTERED DATE _____

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

V. European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

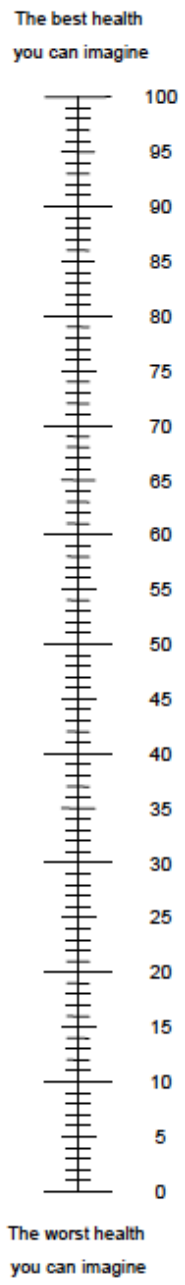
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



VI. Medication Adherence Report Scale (MARS)

QUESTIONS ABOUT USING YOUR MEDICINES

- Many people find a way of using their medicines that suits them
- This may differ from the instructions on the label or from what their doctor has said
- We would like to ask you a few questions about how you use your medicines

Here are some ways in which people have said that they use their medicines

For each of these statements, please tick the box which best applies to you

	Your own way of using your medicines	Always	Often	Sometimes	Rarely	Never
M1	I forget to take them					
M2	I alter the dose					
M3	I stop taking them for a while					
M4	I decide to miss out a dose					
M5	I take less than instructed					
M6	I take more than instructed					

VII. Beliefs about Medicines Questionnaire (BMQ)

BMQ-S11_G8 Project Number .....

YOUR VIEWS ABOUT
MEDICINES PRESCRIBED FOR YOU

- We would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people have made about their medicines.
- Please show how much you agree or disagree with them by ticking the appropriate box.

There are no right or wrong answers.
We are interested in your personal views

	Views about MEDICINES PRESCRIBED FOR YOU:	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
	My health, at present, depends on my medicines					
	Having to take medicines worries me					
	My life would be impossible without my medicines					
	I sometimes worry about long-term effects of my medicines					
	Without my medicines I would be very ill					
	My medicines are a mystery to me					
	My health in the future will depend on my medicines					
	My medicines disrupt my life					
	I sometimes worry about becoming too dependent on my medicines					
	My medicines protect me from becoming worse					
	These medicine give me unpleasant side effects					

YOUR VIEWS ABOUT
MEDICINES IN GENERAL

- These are statements that other people have made about medicines in general.
- Please show how much you agree or disagree with them by ticking the appropriate box.

	Views about MEDICINES IN GENERAL	Strongly Agree	Agree	Uncertain	Disagree	Strongly Disagree
	Doctors use too many medicines					
	People who take medicines should stop their treatment for a while every now and again					
	Most medicines are addictive					
	Natural remedies are safer than medicines					
	Medicines do more harm than good					
	All medicines are poisons					
	Doctors place too much trust on medicines					
	If doctors had more time with patients they would prescribe fewer medicines					

Appendix 11. Confirmation of Ethical Opinion

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Humber Bridge
Yorkshire and the Humber Research Ethics Office
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Telephone: 0113 3050127
Facsimile: 0113 8556191

05 July 2012

Mr Toby Capstick
Lead Respiratory Pharmacist
Leeds Teaching Hospitals NHS Trust
Pharmacy Department
St James's University Hospital
Beckett Street, Leeds
LS9 7TF

Dear Mr Capstick

Study title:	**The Effectiveness of Pharmacist interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma**
REC reference:	**12/YH/0259**
Protocol number:	**n/a**

Thank you for your letter of 29 June 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		01 May 2012
Investigator CV		29 March 2012
Letter from Sponsor		13 April 2012
Letter from Statistician		20 February 2012
Letter of invitation to participant	1	28 February 2012
Other: Julie Morgan CV		29 March 2012
Other: Alison Blenkinsopp CV		
Other: Community Pharmacist Letter UC Group	1	28 February 2012
Other: Community Pharmacist Letter PI Group	1	28 February 2012
Other: Letter from Robbie Turner, Chief Executive Officer, Leeds, Bradford & Airedale, Calderdale & Kirklees Local Pharmaceutical Committees		27 March 2012
Other: GP letter	1	28 February 2012
Other: Ian Clifton CV		30 March 2012
Participant Consent Form: PI Group	3	08 June 2012

Participant Consent Form: UC Group	3	08 June 2012
Participant Information Sheet	4	28 June 2012
Protocol	2.1	29 March 2012
Questionnaire: Juniper's Standardised Asthma Quality of Life Questionnaire (AQLQ(S))		
Questionnaire: Juniper's Asthma Control Questionnaire (ACQ)		
Questionnaire: The Medication Adherence Report Scale (MARS) 'Questions about using your medicines'		
Questionnaire: Beliefs about Medicines (BMQ)		
Questionnaire: EQ-5D-5L		
REC application		29 March 2012
Referees or other scientific critique report		21 March 2012
Response to Request for Further Information		29 June 2012
Summary/Synopsis	1	30 March 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0259	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp
Dr Lynn Cawkwell
Chair

Email: nicola.mallender-ward@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Derek Norfolk, Leeds Teaching Hospitals NHS Trust*

A Research Ethics Committee established by the Health Research Authority

Appendix 12. NHS Permission for Research

The Leeds Teaching Hospitals NHS
NHS Trust

Ref: Amy Dickinson

27/07/2012

Research & Development
Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Mr Toby Capstick
Pharmacy Department
St James' University Hospital
Beckett Street
Leeds
LS9 7TF

Dear Mr Toby Capstick

Re: NHS Permission at LTHT for: The Effectiveness of Pharmacist interventions in Improving Asthma Control and Quality of Life in Patients with Difficult Asthma
LTHT R&D Number: PH10/9328
REC: 12/YH/0259

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at http://www.leedsth.nhs.uk/sites/research_and_development/.

This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

Dr D R Norfolk
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
NHS R&D Form	3.4	29.03.2012
SSI Form	3.4	29.02.2012
Directorate Approval		30.03.2012
REC Letter confirming favourable opinion		05.07.2012
Protocol	2.1	29.03.2012
Information Sheet (REC Approved)	4.0	28.06.2012
Consent Form (REC Approved) *PI Group*	3.0	08.06.2012
Consent Form (REC Approved) *UC Group*	3.0	08.06.2012
Letter of Invitation (REC Approved)	1.0	28.02.2012
GP/Consultant Information Sheet (REC Approved)	1.0	28.02.2012
Summary/Synopsis (REC Approved)	1.0	30.03.2012
Community Pharmacist Letter (REC Approved) *PI Group*	1.0	28.02.2012
Community Pharmacist Letter (REC Approved) *UC Group*	1.0	28.02.2012
Questionnaire (REC Approved) *AQLQ(s)*		*Not Dated*
Questionnaire (REC Approved) *ACQ*		*Not Dated*
Questionnaire (REC Approved) *MARS*		*Not Dated*
Questionnaire (REC Approved) *BMQ*		*Not Dated*
Questionnaire (REC Approved) *EQ-5D-5L*		*Not Dated*
Letter from Sponsor		13.04.2012
Letter from Statistician		20.02.2012
Peer Review		21.03.2012

Appendix 13. Data Description

Variable	Type of Data	Kolmogorov-Smirnov Asymp. Sig. (2-tailed) (P)	Shape of histogram	P-P Plot	Is the data normal?
Demographic Data					
Age at recruitment	Scale	0.718	Slight Negative skew?	Normal?	Normal
Sex	Nominal	n/a	n/a	n/a	n/a
Duration of asthma instability	Scale	0.001	Positive skewed	Not normal	Not Normal
Steroid courses in previous 12 months	Scale	0.488	Slight Positive skew?	Normal?	Normal
Hospital admissions and A&E visits in previous 12 months	Scale	0.000	Positive skewed	Not normal	Not Normal
Prescribed medication	Nominal	n/a	n/a	n/a	n/a
Steroid courses in previous 3 months at baseline	Scale	0.068	Positive skewed	Not normal?	Not Normal
Steroid courses in previous 3 Months at follow up	Scale	0.002	Positive skewed	Not normal	Not Normal
Hospital admissions in previous 3 Months at baseline	Scale	0.000	Positive skewed	Not normal?	Not Normal
Hospital admissions in previous 3 Months at follow up	Scale	0.000	Positive skewed	Not normal?	Not Normal
FEV_1 at baseline	Scale	0.981	Normal	Normal	Normal
FEV_1 at follow up	Scale	0.948	Normal	Normal	Normal
FEV_1/FVC at baseline	Scale	0.909	Normal	Normal	Normal
FEV_1/FVC at follow up	Scale	0.710	Normal	Normal	Normal
FeNO at baseline	Scale	0.178	Positive skewed	Not normal	Not Normal
FeNO at follow up	Scale	0.137	Positive skewed	Not normal	Not Normal
Smoking status	Nominal	n/a	n/a	n/a	n/a
Possession of asthma action plan	Nominal	n/a	n/a	n/a	n/a
Beclometasone-CFC dose at baseline	Scale	0.002	Positive skewed	Positive skewed	Not Normal
Beclometasone-CFC dose at follow up	Scale	0.001	Positive skewed	Positive skewed	Not Normal
SABA use per week at baseline	Scale	0.041	Positive skewed	Positive skewed	Not Normal
SABA use per week at follow up	Scale	0.013	Positive skewed	Positive skewed	Not Normal
Asthma control and quality of life data					
ACQ	Ordinal	n/a	n/a	n/a	n/a
AQLQ(S)	Ordinal	n/a	n/a	n/a	n/a
ED-5Q-5L	Ordinal	n/a	n/a	n/a	n/a
ED-5Q-5L-vas at baseline	Scale	0.609	Negatively skewed?	Normal	Normal
ED-5Q-5L-vas at follow up	Scale	0.589	Normal	Normal	Normal
MARs data					
MARs questions	Ordinal	n/a	n/a	n/a	n/a
BMQ data					
BMQ questions	Ordinal	n/a	n/a	n/a	n/a
Inhaler technique – Inspiratory Flow					
pMDI technique at baseline *before* education	Scale	0.650	Normal	Normal	Normal

Variable	Type of Data	Kolmogorov -Smirnov Asymp. Sig. (2-tailed) (P)	Shape of histogram	P-P Plot	Is the data normal?
pMDI technique at baseline *after* education	Scale	0.135	Normal	Not normal?	Normal
Accuhaler technique at baseline *before* education	Scale	0.418	Bimodal?	Not normal	Not Normal
Accuhaler technique at baseline *after* education	Scale	0.742	Normal	Not normal?	Normal
Turbohaler technique at baseline *before* education	Scale	0.355	Positive skewed?	Normal	Normal
Turbohaler technique at baseline *after* education	Scale	0.541	Normal	Normal	Normal
HandiHaler technique at baseline *before* education	Scale	0.101	Positive skewed?	Not normal	Not Normal
HandiHaler technique at baseline *after* education	Scale	no data	no data	no data	n/a
Easi-Breathe technique at baseline *before* education	Scale	0.787	Positive skewed?	no data	n/a
Easi-Breathe technique at baseline *after* education	Scale	0.107	Positive skewed?	no data	n/a
pMDI technique at follow up *before* education	Scale	0.493	Positive skewed?	Normal?	Not Normal
pMDI technique at follow up *after* education	Scale	0.011	Positive skewed?	Not normal	Not Normal
Accuhaler technique at follow up *before* education	Scale	0.970	Normal	Normal	Normal
Accuhaler technique at follow up *after* education	Scale	0.500	Bimodal	Not normal?	Not Normal
Turbohaler technique at follow up *before* education	Scale	0.324	Negative skewed?	Not normal?	Not Normal
Turbohaler technique at follow up *after* education	Scale	1.000	Insufficient data	Normal	Normal
HandiHaler technique at follow up *before* education	Scale	0.826	Insufficient data	Normal	Normal
HandiHaler technique at follow up *after* education	Scale	no data	Normal	no data	n/a
Easi-Breathe technique at follow up *before* education	Scale	0.573	Positive skewed?	Normal	Normal
Easi-Breathe technique at follow up *after* education	Scale	0.923	Normal	Normal	Normal
Inhaler Technique Training and Patient Preference					
Type of healthcare professional who has previous provided inhaler technique training	Nominal	n/a	n/a	n/a	n/a
Inhaler device preference	Nominal	n/a	n/a	n/a	n/a
Inhaler technique training - inhaler technique scores					
Inhaler technique score, by device at baseline, at t-MUR, and at follow up	Ordinal	n/a	n/a	n/a	n/a
Inhaler technique training - total number of errors in technique (baseline data presented only)					
pMDI total errors at baseline *before* education	Scale	0.022	Positive skewed?	Normal?	Not Normal
pMDI total errors at baseline *after* education	Scale	0.000	Positive skewed	Not normal?	Not Normal
Accuhaler total errors at baseline *before* education	Scale	0.010	Positive skewed	Not normal	Not Normal
Accuhaler total errors at baseline *after* education	Scale	0.000	Positive skewed	Not normal	Not Normal

Variable	Type of Data	Kolmogorov-Smirnov Asymp. Sig. (2-tailed) (P)	Shape of histogram	P-P Plot	Is the data normal?
Turbohaler total errors at baseline *before* education	Scale	0.007	Positive skewed	unclear	Not Normal
Turbohaler total errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
Easi-Breathe total errors at baseline *before* education	Scale	0.580	Negative Skewed	unclear	Not Normal
Easi-Breathe total errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
Easyhaler total errors at baseline *before* education	Scale	0.491	Positive skewed	Not normal	Not Normal
Easyhaler total errors at baseline *after* education	Scale	0.001	Positive skewed	unclear	Not Normal
HandiHaler total errors at baseline *before* education	Scale	0.510	Normal?	Normal	Normal
HandiHaler total errors at baseline *after* education	Scale	0.000	Positive skewed	Not normal	Not Normal
Respimat total errors at baseline *before* education	Scale	0.972	Positive skewed	Not normal	Not Normal
Respimat total errors at baseline *after* education	Scale	0.088	Positive skewed	Not normal	Not Normal
Spacer (Multiple Inhalation Technique) total errors at baseline *before* education	Scale	0.953	Negative skewed?	unclear	Insufficient data
Spacer (Multiple Inhalation Technique) total errors at baseline *after* education	Scale	0.110	Positive skewed	unclear	Insufficient data
Spacer (Single Inhalation Technique) total errors at baseline *before* education	Scale	0.218	Positive skewed	Not normal	Insufficient data
Spacer (Single Inhalation Technique) total errors at baseline *after* education	Scale	no data	Normal?	unclear	Insufficient data
Inhaler technique training - number of critical errors in technique (baseline data presented only)					
pMDI critical errors at baseline *before* education	Scale	0.008	Negative Skewed	unclear	Not Normal
pMDI critical errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
Accuhaler critical errors at baseline *before* education	Scale	0.001	Positive skewed	unclear	Not Normal
Accuhaler critical errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
Turbohaler critical errors at baseline *before* education	Scale	0.001	Positive skewed	unclear	Not Normal
Turbohaler critical errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
Easi-Breathe critical errors at baseline *before* education	Scale	0.000	Negative Skewed	unclear	Not Normal
Easi-Breathe critical errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
Easyhaler critical errors at baseline *before* education	Scale	0.682	Positive skewed	unclear	Insufficient data
Easyhaler critical errors at baseline *after* education	Scale	0.000	Positive skewed	unclear	Not Normal
HandiHaler critical errors at baseline *before* education	Scale	0.170	Positive skewed / Bimodal	unclear	Not Normal
HandiHaler critical errors at	Scale	0.000	Positive	unclear	Not

Variable	Type of Data	Kolmogorov-Smirnov Asymp. Sig. (2-tailed) (P)	Shape of histogram	P-P Plot	Is the data normal?
baseline *after* education			skewed		Normal
Respimat critical errors at baseline *before* education	Scale	0.941	Normal?	unclear	Normal
Respimat Baseline critical errors at baseline *after* education	Scale	0.016	Positive skewed	unclear	Not Normal
Spacer (Multiple Inhalation Technique) critical errors at baseline *before* education	Scale	0.933	Bimodal	unclear	Not Normal
Spacer (Multiple Inhalation Technique) critical errors at baseline *after* education	Scale	0.272	Positive skewed	unclear	Insufficient data
Spacer (Single Inhalation Technique) critical errors at baseline *before* education	Scale	0.057	Positive skewed	unclear	Not Normal
Spacer (Single Inhalation Technique) critical errors at baseline *after* education	Scale	no data	Normal?	unclear	Insufficient data
Adherence data – GP data					
Number of rescue courses at baseline	Scale	0.025	Positive skewed	Not normal	Not Normal
Number of rescue courses at follow up	Scale	0.002	Positive skewed	Not normal	Not Normal
Adherence to ICS at baseline	Scale	0.002	Positive skewed	Not normal	Not Normal
Adherence to ICS at follow up	Scale	0.003	Positive skewed	Not normal	Not Normal
Use of inhaler devices at baseline					
Device(s) prescribed at baseline	Nominal	n/a			
Total number of devices prescribed	Scale	0.000	Positive skewed	Not normal	Not Normal

Appendix 14. Effect of education on inhaler technique score (% of each step performed correctly) at baseline, before and after education for all inhaler devices used.

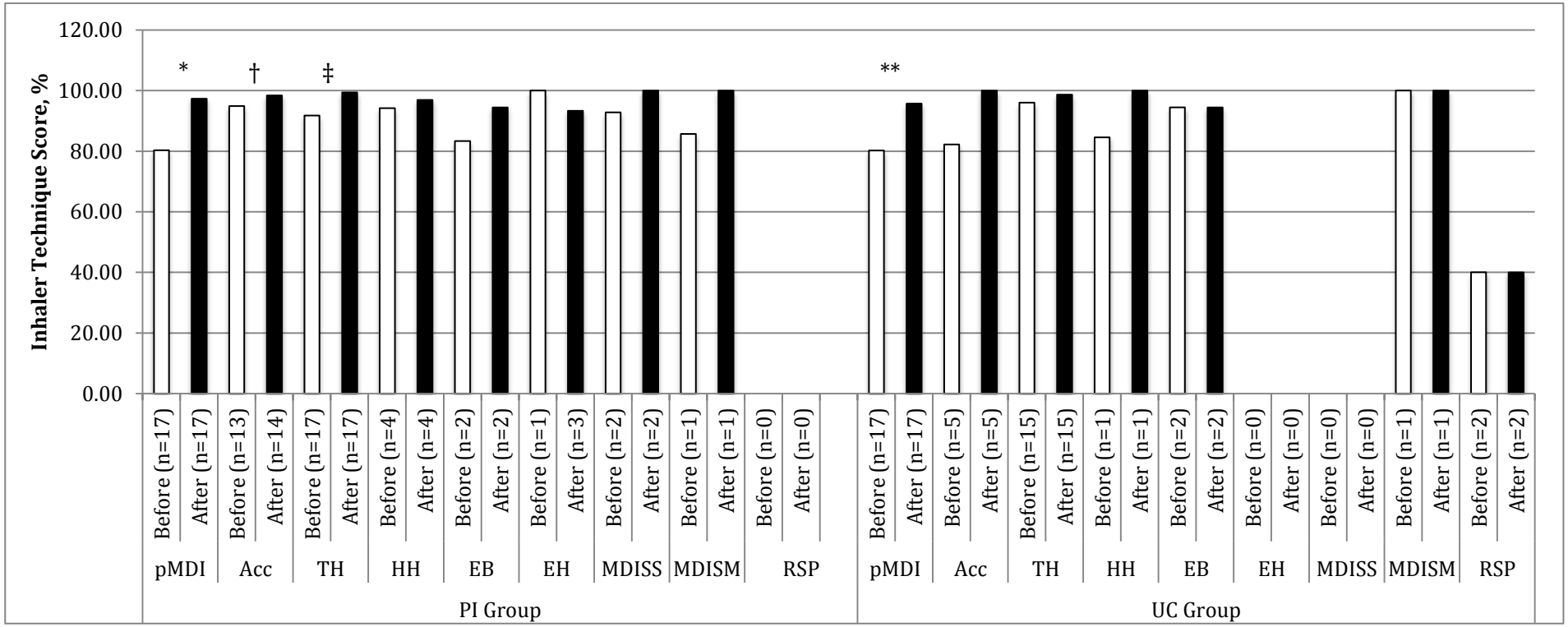


Figure 20. Effect of education on inhaler technique score (% of each step performed correctly) at baseline, before and after education for all inhaler devices used (complete data).

PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; HH; HandiHaler; EB, Easi-Breathe; EH, Easyhaler; MDISS, pMDI + spacer (single-breath method); MDISM, pMDI + spacer (multiple-breath method); RSP, Respimat. Improvements in inhaler technique assessed using Wilcoxon test. Difference in inhaler technique score before and after education: *p<0.001; †p=0.034; ‡p=0.001; **p=0.012.

Appendix 15. Effect of education on the proportion of patients with optimal, satisfactory, or unsatisfactory inhaler technique at baseline, for all inhaler devices used.

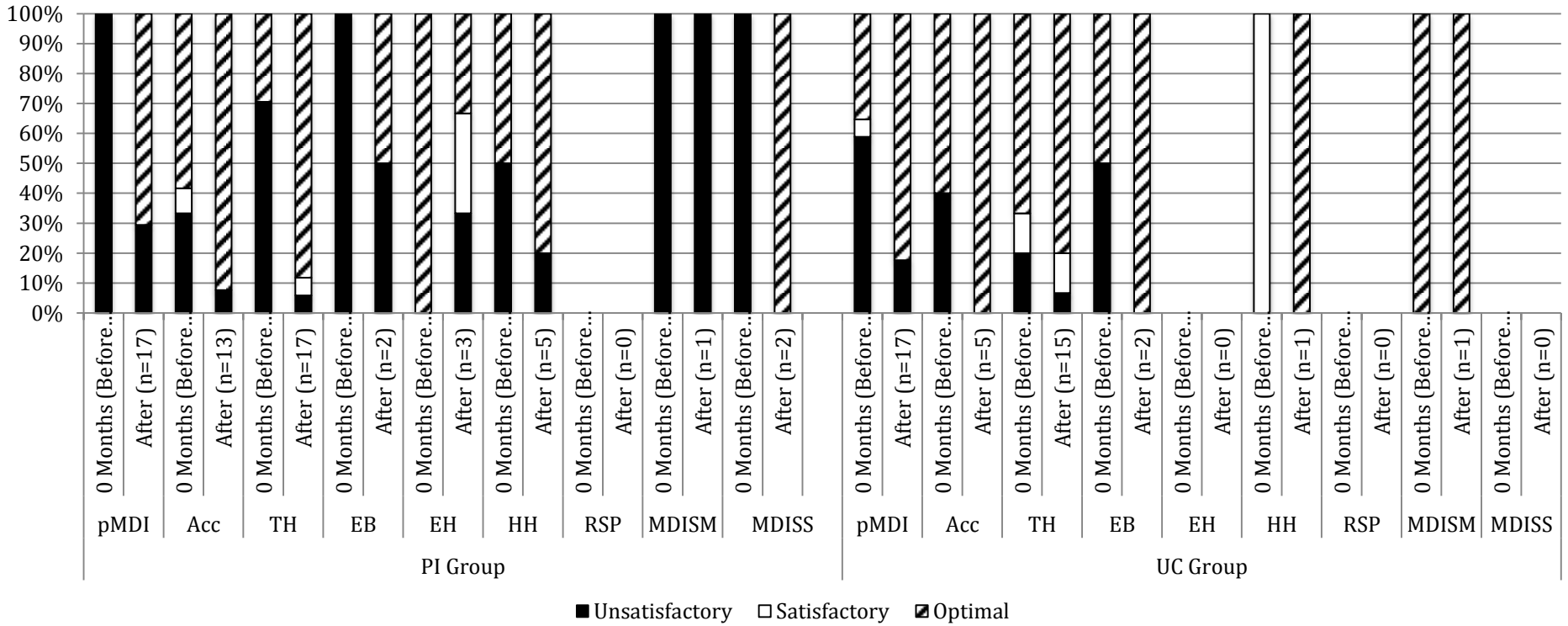


Figure 21. Effect of education on the proportion of patients with optimal, satisfactory, or unsatisfactory inhaler technique at baseline, for all inhaler devices used (complete data).
Optimal technique is defined as no errors using inhaler device; satisfactory inhaler technique is defined as making some minor bur no critical errors; unsatisfactory inhaler technique is defined as making at least one critical error. PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; EB, Easi-Breathe; EH, Easyhaler; HH; HandiHaler; RSP, Respimat; MDISM, pMDI + spacer (multiple-breath method); MDISS, pMDI + spacer (single-breath method).

Appendix 16. Effect of education on inhaler technique score (% of each step performed correctly) throughout study, for all inhaler devices used.

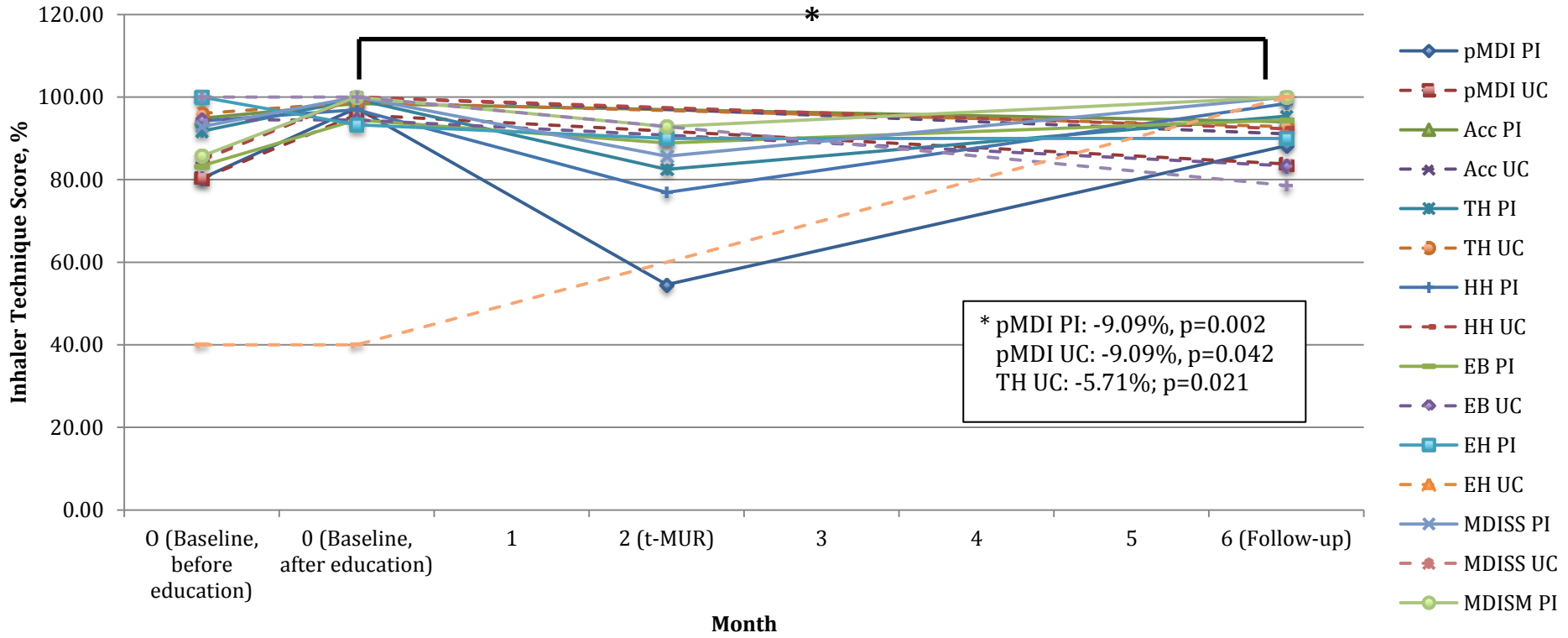


Figure 22. Effect of education on inhaler technique score (% of each step performed correctly) throughout study, for all inhaler devices used (complete data).
PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; HH; HandiHaler; EB, Easi-Breathe; EH, Easyhaler; MDISS, pMDI + spacer (single-breath method); MDISM, pMDI + spacer (multiple-breath method); RSP, Respimat. Improvements in inhaler technique assessed using Wilcoxon test.

Appendix 17. The proportion of patients with optimal, satisfactory, or unsatisfactory inhaler technique throughout the 6-month study, for all inhaler devices used.

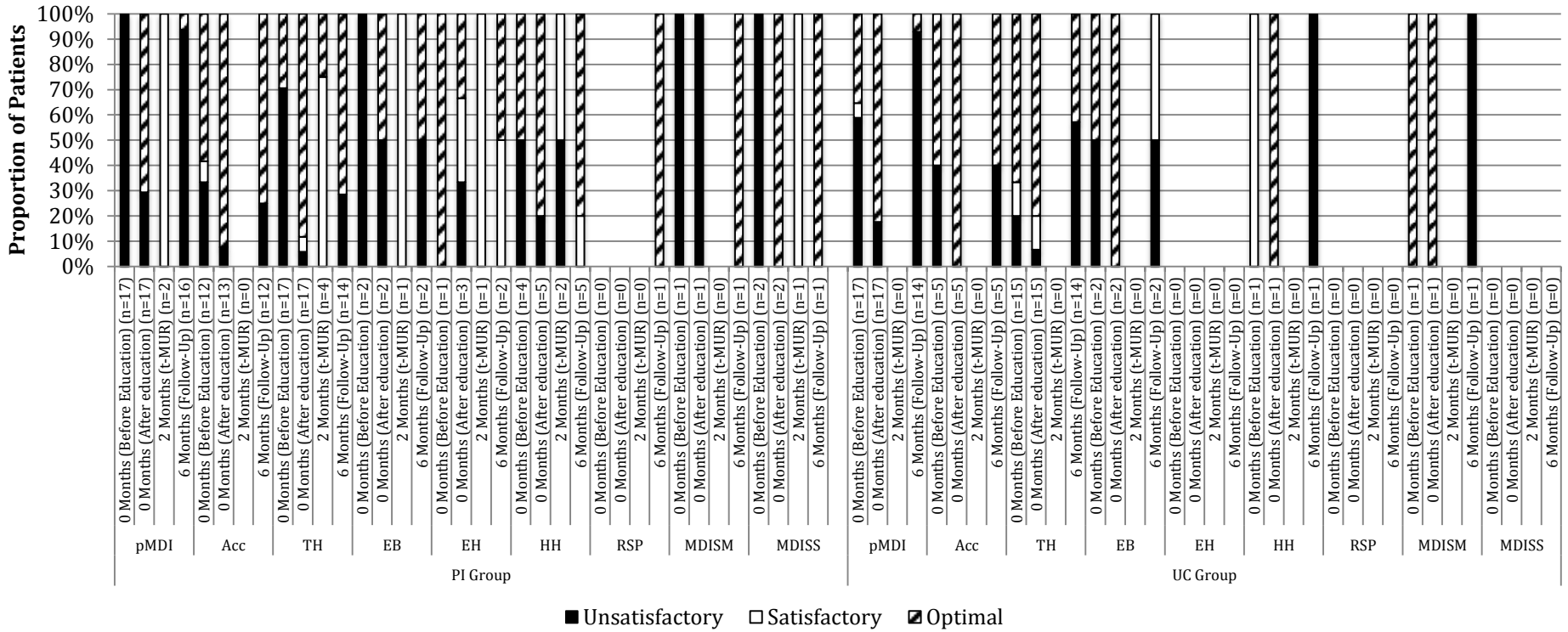


Figure 23. The proportion of patients with optimal, satisfactory, or unsatisfactory inhaler technique throughout the 6-month study, for all inhaler devices used (complete data).

Optimal technique is defined as no errors using inhaler device; satisfactory inhaler technique is defined as making some minor bur no critical errors; unsatisfactory inhaler technique is defined as making at least one critical error. PI, pharmacist intervention group; UC, usual care group; pMDI, pressurised metered dose inhaler; Acc, Accuhaler; TH, Turbohaler; EB, Easi-Breathe; EH, Easyhaler; HH; HandiHaler; RSP, Respimat; MDISM, pMDI + spacer (multiple-breath method); MDISS, pMDI + spacer (single-breath method).

9 References

Adeyeye, O. O. and Onadeko, B. O. (2008) Understanding medication and use of drug delivery device by asthmatic in Lagos. *West African Journal of Medicine,* 27 (3), 155-9.

Adunlin, G. and Mahdavian, S. (2012) The Effectiveness of Pharmacist Interventions on Asthma Management: A Systematic Review. *Journal of Asthma & Allergy Educators,* 3 (6), 264-273.

Al-Showair, R. A., Pearson, S. B. and Chrystyn, H. (2007) The potential of a 2Tone Trainer to help patients use their metered-dose inhalers. *Chest,* 131, 1776-1782.

Alamoudi, O. S. (2003) Pitfalls of inhalation technique in chronic asthmatics. Effect of education program and correlation with peak expiratory flow. *Saudi Medical Journal,* 24 (11), 1205-9.

Ammari, W. G. and Chrystyn, H. (2013) Optimizing the Inhalation Flow and Technique Through Metered Dose Inhalers of Asthmatic Adults and Children Attending a Community Pharmacy. *Journal of Asthma,* 50 (5), 505-513.

Anderson, P. (2005) Patient preference for and satisfaction with inhaler devices. *European Respiratory Review,* 14 (96), 109-116.

Apter, A. J., Wang, X., Bogen, D. K., Rand, C. S., McElligott, S., Polsky, D., Gonzalez, R., Priolo, C., Adam, B., Geer, S. and Ten, T. (2011) Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial. *Journal of Allergy & Clinical Immunology,* 128 (3), 516-23.e1-5.

Armour, C., Bosnic-Anticevich, S., Brillant, M., Burton, D., Emmerton, L., Krass, I., Saini, B., Smith, L. and Stewart, K. (2007) Pharmacy Asthma Care Program (PACP) improves outcomes for patients in the community. *Thorax,* 62 (6), 496-502.

Armour, C. L., Reddel H. K., Lemay K. S., Saini B., Smith L.D., Bosnic-Anticevich S. Z., Song Y. J. C., Alles M. C., Burton D. L., Emmerton L., Stewart K. and I., K. (2013) Feasibility and Effectiveness of an Evidence-Based Asthma Service in Australian Community Pharmacies: A Pragmatic Cluster Randomized Trial. *Journal of Asthma,* 50 (3), 302-309.

Asselin, M. E. (2003) Insider research: issues to consider when doing qualitative research in your own setting. *Journal for nurses in staff development,* 19 (2), 99-103.

Asthma UK (Undated) *Asthma facts and FAQs.* London, UK: Asthma UK. Available from: http://www.asthma.org.uk/asthma-facts-and-statistics (Accessed 31.8.14).

Axelsson, M., Cliffordson, C., Lundback, B. and Lotvall, J. (2013) The function of medication beliefs as mediators between personality traits and adherence behavior in people with asthma. *Patient Prefer Adherence,* 7, 1101-9.

Axelsson, M., Emilsson, M., Brink, E., Lundgren, J., Toren, K. and Lotvall, J. (2009) Personality, adherence, asthma control and health-related quality of life in young adult asthmatics. *Respir Med,* 103 (7), 1033-40.

Axelsson, M., Lotvall, J., Lundgren, J. and Brink, E. (2011) Motivational foci and asthma medication tactics directed towards a functional day. *BMC Public Health,* 11.

Azouz, W. and Chrystyn, H. (2012) Clarifying the dilemmas about inhalation techniques for dry powder inhalers: integrating science with clinical practice. *Primary Care Respiratory Journal,* 21 (2), 208-213.

Baddar, S., Jayakrishnan, B. and Al-Rawas, O. A. (2014) Asthma control: importance of compliance and inhaler technique assessments. *J Asthma,* Early Online**,** 1-6. DOI: 10.3109/02770903.2013.871558

Baddar, S. A., Al-Rawas, O. A., Al-Riyami, K. A., Worthing, E. A., Hanssens, Y. I., Taqi, A. M. and Al-Riyami, B. M. S. (2001) Metered-dose inhaler technique among healthcare providers practising in Oman. *SQU Journal for Scientific Research Medical Sciences,* 1**,** 39-43.

Bagole, L. E., Beaumont, A. and Morgan, I. (2007) Outcomes of medicines use reviews for people with asthma. *Int J Pharm Pract,* 15 (Suppl 2)**,** B66.

Bailey, W. C., Richards, J. M., Jr, Brooks, C., Soong, S., Windsor, R. A. and Manzella, B. A. (1990) A randomized trial to improve self-management practices of adults with asthma. *Archives of Internal Medicine,* 150 (8)**,** 1664-1668.

Barbanel, D., Eldridge, S. and Griffiths, C. (2003) Can a self-management programme delivered by a community pharmacist improve asthma control? A randomised trial. *Thorax,* 58 (10)**,** 851-4.

Barnes, P. J. and Woolcock, A. J. (1998) Difficult asthma. *European Respiratory Journal,* 12 (5)**,** 1209-1218.

Basheti, I. A., Armour, C. L., Bosnic-Anticevich, S. Z. and Reddel, H. K. (2008) Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. *Patient Educ Couns,* 72 (1)**,** 26-33.

Basheti, I. A., Armour, C. L., Reddel, H. K. and Bosnic-Anticevich, S. Z. (2009) Long-term maintenance of pharmacists' inhaler technique demonstration skills. *American Journal of Pharmaceutical Education,* 73 (2).

Basheti, I. A., Bosnic-Anticevich, S. Z., Armour, C. L. and Reddel, H. K. (2014) Checklists for Powder Inhaler Technique: A Review and Recommendations. *Respiratory Care,* 59 (7)**,** 1140-1154.

Basheti, I. A., Qunaibi, E., Bosnic-Anticevich, S. Z., Armour, C. L., Khater, S., Omar, M. and Reddel, H. K. (2011) User error with Diskus and Turbuhaler by asthma patients and pharmacists in Jordan and Australia. *Respiratory Care,* 56 (12)**,** 1916-23.

Basheti, I. A., Reddel, H. K., Armour, C. L. and Bosnic-Anticevich, S. Z. (2005) Counseling about turbohaler technique: needs assessment and effective strategies for community pharmacists. *Respir Care,* 50 (5)**,** 617-623.

Basheti, I. A., Reddel, H. K., Armour, C. L. and Bosnic-Anticevich, S. Z. (2007) Improved asthma outcomes with a simple inhaler technique intervention by community pharmacists. *Journal of Allergy & Clinical Immunology,* 119 (6)**,** 1537-8.

Bateman, E. D., Boushey, H. A., Bousquet, J., Busse, W. W., Clark, T. J. H., Pauwels, R. A. and Pedersen, S. E. (2004) Can Guideline-defined Asthma Control be Achieved? The Gaining Optimal Asthma ControL Study. *Am J Respir Crit Care Med,* 170**,** 836-44.

Bateman, E. D., Bousquet, J., Busse, W. W., Clark, T. J., Gul, N., Gibbs, M. and Pedersen, S. (2008) Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma controL (GOAL) study. *Allergy,* 63 (7)**,** 932-8.

Baverstock, M., Woodhall, N. and Maarman, V. (2010) P94 Do healthcare professionals have sufficient knowledge of inhaler techniques in order to educate their patients effectively in their use? *Thorax,* 65 (Suppl 4)**,** A117-A118.

Bell, J. (2008) Why Optimise inhaler technique in asthma and COPD. *British Journal of Primary Care Nursing,* 2 (2), 37-39.

Benavides, S., Rodriguez, J. C. and Maniscalco-Feichtl, M. (2009) Pharmacist involvement in improving asthma outcomes in various healthcare settings: 1997 to present. *Ann Pharmacother,* 43 (1), 85-97.

Bender, B. G., Apter, A., Bogen, D. K., Dickinson, P., Fisher, L., Wamboldt, F. S. and Westfall, J. M. (2010) Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. *Journal of the American Board of Family Medicine: JABFM,* 23 (2), 159-65.

Berry, M. A., Shaw, D. E., Green, R. H., Brightling, C. E., Wardlaw, A. J. and Pavord, I. D. (2005) The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clinical & Experimental Allergy,* 35 (9), 1175-1179.

Biddiscombe, M. F., Usmani, O. S. and Barnes, P. J. (2003) A system for the production and delivery of monodisperse salbutamol aerosols to the lungs. *International Journal of Pharmaceutics,* 254 (2), 243-253.

Blenkinsopp, A. (2010) Time to take stock of medicine use review. *Pharmaceutical Journal,* 285, 434.

Blenkinsopp, A., Bond, C., Celino, G., Inch, J. and Gray, N. (2008) Medicines Use Review: adoption and spread of a service innovation. *int J Pharm Pract,* 16 (4), 271-276.

Blenkinsopp, A., Celino, G., Bond, C. and Inch, J. (2007) Medicines use reviews: the first year of a new community pharmacy service. *Pharmaceutical Journal,* 278, 218-223.

Boise, E. (2014) Patient Education and Designing an Asthma Action Plan. *Otolaryngologic clinics of North America,* 47 (1), 127-134.

Bolman, C., Arwert, T. G. and Vollink, T. (2011) Adherence to prophylactic asthma medication: habit strength and cognitions. *Heart & Lung,* 40 (1), 63-75.

Borgström, L., Bondesson, E., Morén, F., Trofast, E. and Newman, S. P. (1994) Lung deposition of budesonide inhaled via Turbuhaler®: a comparison with terbutaline sulphate in normal subjects. *European Respiratory Journal,* 7 (1), 69-73.

Bousquet, J., Mantzouranis, E., Cruz, A. A., Aït-Khaled, N., Baena-Cagnani, C. E., Bleecker, E. R., Brightling, C. E., Burney, P., Bush, A., Busse, W. W., Casale, T. B., Chan-Yeung, M., Chen, R., Chowdhury, B., Chung, K. F., Dahl, R., Drazen, J. M., Fabbri, L. M., Holgate, S. T., Kauffmann, F., Haahtela, T., Khaltaev, N., Kiley, J. P., Masjedi, M. R., Mohammad, Y., O'Byrne, P., Partridge, M. R., Rabe, K. F., Togias, A., van Weel, C., Wenzel, S., Zhong, N. and Zuberbier, T. (2010) Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma. *Journal of Allergy and Clinical Immunology,* 126 (5), 926-938.

Bowling, A. (2002) *Research Methods In Health: Investigating Health and Health Services.* McGraw-Hill Education.

Brennan, V. K., Osman, L. M., Graham, H., Critchlow, A. and Everard, M. L. (2005) True device compliance: the need to consider both competence and contrivance. *Respir Med,* 99 (1), 97-102.

British Thoracic Society and Scottish Intercollegiate Guidelines Network (2014) *British guideline on the management of asthma: a national clinical guideline.* London, UK: British Thoracic Society. Available from: http://www.brit-thoracic.org.uk/

British Thoracic Society Standards of Care Committee (2008) BTS statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease. *Thorax,* 63 (Suppl 1)**,** i1-i16.
Brocklebank, D., Ram, F., Wright, J., Barry, P. and Cates, C. (2001) Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technology Assessment,* 5 (26)**,** 1-155.
Brooks, R. (1996) EuroQol: the current state of play. *Health Policy,* 37 (1)**,** 53-72.
Cain, W. T., G., C. and Oppenheimer, J. J. (2001) The ability of the community pharmacist to learn the proper actuation techniques of inhaler devices. *Journal of Allergy & Clinical Immunology,* 108 (6)**,** 918-920.
Campbell, M. J. and Machin, D. (1999) *Medical statistics: A commonsense approach.* Third edition ed*.* Chichester, England: Wiley.
Campos, A., Reyes, J. and Torres, M. (2006) Therapeutic compliance among asthma patients in an allergy clinic: third evaluation (SEGARIA Project). *Allergologia et Immunopathologia,* 34 (4)**,** 141-5.
Capstick, T., Clifton, I., Morgan, J., Silcock, J. and Blenkinsopp, A. (2013) Inhaler technique: An unmet need in patients with difficult asthma? *European Respiratory Journal,* 42 (Suppl 57)**,** P700.
Capstick, T. G. D. and Clifton, I. J. (2012) Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. *Expert Rev Respir Med,* 6 (1)**,** 91-103.
Capstick, T. G. D., Clifton, I. J., Morgan, J. and Blenkinsopp, A. (2012) Medicines Use Reviews: an unmet need in difficult asthma. *Clinical Pharmacist,* Suppl 3**,** S43-S44.
Celino, G., Gray, N., Blenkinsopp, A., Bond, C. and Inch, J. (2007) General practitioners' experiences of medicines use review: qualitative findings from the national evaluation of the community pharmacy contractual framework in England and Wales. *int J Pharm Pract,* 15 ((Suppl 2))**,** B20-B21.
Chan, A. H. Y., Reddel, H. K., Apter, A., Eakin, M., Riekert, K. and Foster, J. M. (2013) Adherence Monitoring and E-Health: How Clinicians and Researchers Can Use Technology to Promote Inhaler Adherence for Asthma. *Journal of Allergy and Clinical Immunology: In Practice,* 1 (5)**,** 446-454.
Charrois, T., Newman, S., Sin, D., Senthilselvan, A. and Tsuyuki, R. T. (2004) Improving asthma symptom control in rural communities: the design of the Better Respiratory Education and Asthma Treatment in Hinton and Edson study. *Control Clin Trials,* 25 (5)**,** 502-14.
Charrois, T., Newman, S. C., Senthilselvan, A. and Tsuyuki, R. T. (2006) Improving asthma control in the rural setting: The BREATHE (Better Respiratory Education and Asthma Treatment in Hinton and Edson) study. *Can Pharm J,* 139 (4)**,** 44-50.
Chorão, P., Pereira, A. M. and Fonseca, J. A. (2014) Inhaler devices in asthma and COPD – An assessment of inhaler technique and patient preferences. *Respiratory Medicine,* 108 (7)**,** 968-975.
Chrystyn, H. (2003) Is inhalation rate important for a dry powder inhaler? Using the In-Check Dial to identify these rates. *Respir Med,* 97 (2)**,** 181-7.
Chrystyn, H. and Price, D. (2009) Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Care Respir J,* 18 (4)**,** 243-9.
Chung, K. F., Wenzel, S. E., Brozek, J. L., Bush, A., Castro, M., Sterk, P. J., Adcock, I. M., Bateman, E. D., Bel, E. H., Bleecker, E. R., Boulet, L. P., Brightling, C., Chanez,

P., Dahlen, S. E., Djukanovic, R., Frey, U., Gaga, M., Gibson, P., Hamid, Q., Jajour, N. N., Mauad, T., Sorkness, R. L. and Teague, W. G. (2014) International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal,* 43 (2)**,** 343-373.

Clancy, M. J. (2002) Overview of research designs. *Emergency Medicine Journal,* 19**,** 546-549.

Clark, N. M., Cabana, M. D., Nan, B., Gong, Z. M., Slish, K. K., Birk, N. A. and Kaciroti, N. (2008) The Clinician-Patient Partnership Paradigm: Outcomes Associated With Physician Communication Behavior. *Clinical Pediatrics,* 47 (1)**,** 49-57.

Clark, N. M., Ko, Y. A., Gong, Z. M. and Johnson, T. R. (2012) Outcomes associated with a negotiated asthma treatment plan. *Chronic Respiratory Disease,* 9 (3)**,** 175-182.

Clerisme-Beaty, E. M., Bartlett, S. J., Teague, W. G., Lima, J., Irvin, C. G., Cohen, R., Castro, M., Wise, R. A. and Rand, C. S. (2011) The Madison Avenue effect: how drug presentation style influences adherence and outcome in patients with asthma. *Journal of Allergy & Clinical Immunology,* 127 (2)**,** 406-11.

Cochrane, G. M., Horne, R. and Chanez, P. (1999) Compliance in Asthma. *Respir Med,* 93**,** 763-9.

Cochrane, M. G., Bala, M. V., Downs, K. E., Mauskopf, J. and Ben-Joseph, R. H. (2000) Inhaled Corticosteroids for Asthma Therapy: Patient Compliance, Devices, and Inhalation Technique. *Chest,* 117 (2)**,** 542-550.

Cordina, M., McElnay, J. C. and Hughes, C. M. (2001) Assessment of a community pharmacy-based program for patients with asthma. *Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy,* 21 (10)**,** 1196-203.

Craig, P., Dieppe, P., MacIntyre, S., Michie, S., Nazareth, I., Petticrew, M. and Council., O. b. o. t. M. R. (2008) *Developing and evaluating complex interventions: new guidance.* Medical Research Council,

Crompton, G. K., Barnes, P. J., Broeders, M., Corrigan, C., Corbetta, L., Dekhuijzen, R., Dubus, J. C., Magnan, A., Massone, F., Sanchis, J., Viejo, J. L., Voshaar, T. and Aerosol, D. T. (2006) The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team. *Respir Med,* 100 (9)**,** 1479-94.

Das Gupta, R. and Guest, J. F. (2003) Factors affecting UK primary-care costs of managing patients with asthma over 5 years. *Pharmacoeconomics,* 21 (5)**,** 357-369.

Department of Health (2010) *Equity and excellence: liberating the NHS.* London, UK: Department of Health.

Department of Health (2011) *An Outcomes Strategy for Chronic Obstructive Pulmonary Disease (COPD) and Asthma.* London, UK: Department of Health.

Department of Health (2013) *The National Health Service Act 2006: The Pharmaceutical Services (Advanced and Enhanced Services) (England) Directions 2013.* London, UK: Department of Health.

DiBello, K. K., Boyar, K. L., Abrenica, S. C. and Worral, P. S. (2013) The effectiveness of text messaging programs on adherence to treatment regimens among adults aged 18 to 45 years diagnosed with asthma: a systematic review protocol. *JBI Database of Systematic Reviews & Implementation Reports,* 11 (8)**,** 170-185.

Dolovich, M. B., Ahrens, R. C., Hess, D. R., Anderson, P., Dhand, R., Rau, J. L., Smaldone, G. C. and Guyatt, G. (2005) Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest

Physicians/American College of Asthma, Allergy, and Immunology. *Chest,* 127 (1), 335-71.
Donaldson, B., Lachowicz, M. F., Stonerook, E. A. and Bushardt, R. L. (2013) Rethinking asthma education: A practical approach to improve treatment outcomes. *Journal of the American Academy of Physician Assistants,* 26 (6), 15-20.
Douglass, J. A., Goeman, D. P., McCarthy, E. A., Sawyer, S. M., Aroni, R. A., Stewart, K. and Abramson, M. J. (2012) Over-the-counter beta2-agonist purchase versus script: a cross-sectional study. *Respir Med,* 106 (2), 223-9.
Easthall, C., Song, F. and Bhattacharya, D. (2013) A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. *BMJ Open,* 3 (8), e002749.
Emilsson, M., Berndtsson, I., Lotvall, J., Millqvist, E., Lundgren, J., Johansson, A. and Brink, E. (2011) The influence of personality traits and beliefs about medicines on adherence to asthma treatment. *Primary Care Respiratory Journal,* 20 (2), 141-7.
Emmerton, L., Shaw, J. and Kheir, N. (2003) Asthma management by New Zealand pharmacists: a pharmaceutical care demonstration project. *Journal of Clinical Pharmacy and Therapeutics,* 28 (5), 395-402.
Engelkes, M., Janssens, H. M., De Jongste, J. C. S., M.C.J.M. and Verhamme, K. M. C. (2013) Medication adherence and severe asthma exacerbations: Systematic review. *Pharmacoepidemiology and Drug Safety,* 22 (s1), 110-111.
Esposti, L. D., Saragoni, S., Benemei, S., Batacchi, P., Geppetti, P., Di Bari, M., Marchionni, N., Sturani, A., Buda, S. and Esposti, E. D. (2011) Adherence to antihypertensive medications and health outcomes among newly treated hypertensive patients. *ClinicoEconomics and Outcomes Research,* 3, 47-54.
Everard, M. L. (2001) Guidelines for devices and choices. *J Aerosol Med,* 14 (suppl 1), S59-S64.
Gamble, J., Stevenson, M. and Heaney, L. G. (2011) A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med,* 105 (9), 1308-15.
Gamble, J., Stevenson, M., McClean, E. and Heaney, L. G. (2009) The prevalence of nonadherence in difficult asthma. *American Journal of Respiratory & Critical Care Medicine,* 180 (9), 817-22.
Garcia-Cardenas, V., Sabater-Hernandez, D., Kenny, P., Martinez-Martinez, F., Faus, M. J. and Benrimoj, S. I. (2013) Effect of a pharmacist intervention on asthma control. A cluster randomised trial. *Respir Med,* 107 (9), 1346-55.
Gibson, P. G., Powell, H., Wilson, A., Abramson, M. J., Haywood, P., Bauman, A., Hensley, M. J., Walters, E. H. and Roberts, J. J. L. (2002a) Self-management education and regular practitioner review for adults with asthma. *Cochrane Database of Systematic Reviews*, Issue 3. CD001117.
Gibson, P. G., Powell, H., Wilson, A., Hensley, M. J., Abramson, M. J., Bauman, A., Walters, E. H. and Roberts, J. J. L. (2002b) Limited (information only) patient education programs for adults with asthma. *Cochrane Database of Systematic Reviews*, Issue 1. CD001005.
Giraud, V., Allaert, F. A. and Roche, N. (2011) Inhaler technique and asthma: feasability and acceptability of training by pharmacists. *Respir Med,* 105 (12), 1815-22.
Giraud, V. and Roche, N. (2002) Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *European Respiratory Journal,* 19 (2), 246-251.

Glanz, K., Fiel, S. B., Swartz, M. A. and Francis, M. E. (1984) Compliance with an experimental drug regimen for treatment of asthma: its magnitude, importance, and correlates. *J Chron Dis,* 37 (11)**,** 815-24.
Global Initiative for Asthma (2014) *Global Strategy for Asthma Management and Prevention.* Available at: http://www.ginasthma.org/.
Goodyer, L., Savage, I. and Dikmen, Z. (2006) Inhaler technique in Turkish people with poor English: a case of information discrimination? *Pharmacy World & Science,* 28 (2)**,** 107-14.
Greenhalgh, T. (2006) *How to read a paper: The basics of evidence-based medicine.* Massachusetts: Blackwell Publishing.
Hanania, N. A., Wittman, R., Kesten, S. and Chapman, K. R. (1994) Medical personnel's knowledge of and ability to use inhaling devices. Metered-dose inhalers, spacing chambers, and breath-actuated dry powder inhalers. *Chest,* 105 (1)**,** 111-16.
Hardwell, A., Barber, V., Hargadon, T., McKnight, E., Holmes, J. and Levy, M. L. (2011) Technique training does not improve the ability of most patients to use pressurised metered-dose inhalers (pMDIs). *Primary Care Respiratory Journal,* 20 (1)**,** 92-6.
Harnett, C. M., Hunt, E. B., Bowen, B. R., O'Connell, O. J., Edgeworth, D. M., Mitchell, P., Eustace, J. A., Henry, M. T., Kennedy, M. P., Plant, B. J. and Murphy, D. M. (2014) A study to assess inhaler technique and its potential impact on asthma control in patients attending an asthma clinic. *Journal of Asthma,* 51 (4)**,** 440-445.
Haughney, J., Price, D., Barnes, N. C., Virchow, J. C., Roche, N. and Chrystyn, H. (2010) Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs. *Respiratory Medicine,* 104 (9)**,** 1237-1245.
Haughney, J., Price, D., Kaplan, A., Chrystyn, H., Horne, R., May, N., Moffat, M., Versnel, J., Shanahan, E. R., Hillyer, E. V., Tunsater, A. and Bjermer, L. (2008) Achieving asthma control in practice: understanding the reasons for poor control. *Respir Med,* 102 (12)**,** 1681-93.
Haynes, R. B., Ackloo, E., Sahota, N., McDonald, H. P. and Yao, X. (2008) Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews***,** Issue 2. CD000011.
Health and Social Care Information Centre (2014) *Community pharmacy access to Summary Care Records – An Introduction.* Leeds: Available from: http://systems.hscic.gov.uk/scr/staff/scrbasics/scrcommpharmsum.pdf (Accessed 3rd October 2014).
Heaney, L. G., Brightling, C. E., Menzies-Gow, A., Stevenson, M. and Niven, R. M. (2010) Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax,* 65**,** 787-794.
Heaney, L. G., Conway, E., Kelly, C., Johnston, B. T., English, C., Stevenson, M. and Gamble, J. (2003) Predictors of therapy resistant asthma: outcome of a systematic evaluation protocol. *Thorax,* 58 (7)**,** 561-566.
Heaney, L. G. and Horne, R. (2012) Non-adherence in difficult asthma: time to take it seriously. *Thorax,* 67 (3)**,** 268-70.
Higgins, J. P. T. and Green, S. (2011) *Cochrane handbook for systematic reviews. Version 5.1.0 (updated March 2011).* Available from http://www.cochrane-handbook.org: The Cochrane Collaboration.
Hinchageri, S. S., Patil, N., Karan, K., Shalin, i. B. and Swarnakamala, K. (2012) Assessment of medication adherence and factors affecting to medication

adherence in asthma patients by clinical pharmacist. *International Research Journal of Pharmacy,* 3 (3)**,** 211-215.
Holt, S., Suder, A., Weatherall, M., Cheng, S., Shirtcliffe, P. and Beasley, R. (2001) Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysisCommentary: Dosage needs systematic and critical review. *BMJ,* 323 (7307)**,** 253.
Horne, R. (2006) Compliance, adherence, and concordance: implications for asthma treatment. *Chest,* 130 (1 Suppl)**,** 65S-72S.
Horne, R. (2011) Adherence to asthma medication: a question of ability? *Primary Care Respiratory Journal,* 20 (2)**,** 118-9.
Horne, R. and Weinman, J. (1999) Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res,* 6**,** 555-67.
Horne, R. and Weinman, J. (2002) Self-regulation and Self-management in Asthma: Exploring The Role of Illness Perceptions and Treatment Beliefs in Explaining Non-adherence to Preventer Medication. *Psychology & Health,* 17 (1)**,** 17-32.
Horne, R., Weinman, J. and Hankins, M. (1999) The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & Health,* 14 (1)**,** 1-24.
Hoskins, G., McCowan, C., Neville, R. G., Thomas, G. E., Smith, B. and Silverman, S. (2000) Risk factors and costs associated with an asthma attack. *Thorax,* 55**,** 19-24.
Hyland, M. E., Whalley, B., Halpin, D. M. G., Greaves, C. J., Seamark, C., Blake, S., Pinnuck, M., Ward, D., Hawkins, A. and Seamark, D. (2012) Frequency of non-asthma GP visits predicts asthma exacerbations: an observational study in general practice. *Primary Care Respiratory Journal,* 21 (4)**,** 405-411.
Interiano, B. and Guntupalli, K. K. (1993) Metered-dose inhalers: Do health care providers know what to teach? *Archives of Internal Medicine,* 153 (1)**,** 81-85.
Ivanova, J. I., Birnbaum, H. G., Hsieh, M., Yu, A. P., Seal, B., van der Molen, T., Emani, S., Rosiello, R. A. and Colice, G. L. (2008) Adherence to inhaled corticosteroid use and local adverse events in persistent asthma. *American Journal of Managed Care,* 14 (12)**,** 801-809.
Jackevicius, C. A. and Chapman, K. R. (1999) Inhaler education for hospital-based pharmacists: how much is required? *Canadian Respiratory Journal,* 6 (3)**,** 237-44.
James, P. N., Anderson, J. B., Prior, J. G., White, J. P., Henry, J. A. and Cochrane, G. M. (1985) Patterns of drug taking in patients with chronic airflow obstruction. *Postgraduate Medical Journal,* 61 (711)**,** 7-10.
Janson, S. L., McGrath, K. W., Covington, J. K., Cheng, S. C. and Boushey, H. A. (2009) Individualized asthma self-management improves medication adherence and markers of asthma control. *Journal of Allergy & Clinical Immunology,* 123 (4)**,** 840-6.
Jones, J. S., Holstege, C. P., Riekse, R., White, L. and Bergquist, T. (1995) Metered-Dose Inhalers: Do Emergency Health Care Providers Know What to Teach? *Annals of Emergency Medicine,* 26 (3)**,** 308-311.
Juniper, E. F., Bousquet, J., Abetz, L. and Bateman, E. D. (2006) Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med,* 100 (4)**,** 616-21.

Juniper, E. F., Buist, A. S., Cox, F. M., Ferrie, P. F. and King, D. R. (1999a) Validation of a Standardized Version of the Asthma Quality of Life Questionnaire. *Chest,* 115 (5), 1265-1270.

Juniper, E. F., Guyatt, G. H., Epstein, R. S., Ferrie, P. F., Jaeschke, R. and Hiller, T. K. (1992) Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax,* 47, 76-83.

Juniper, E. F., Guyatt, G. H., Ferrie, P. F. and Griffith, L. E. (1993) Measuring Quality of Life in Asthma. *Am J Respir Crit Care Med,* 147 (4), 832-838.

Juniper, E. F., O'Byrne, P. M., Ferrie, P. F., King, D. R. and Roberts, J. N. (2000) Measuring Asthma Control: clinic questionnaire or daily diary? *Am J Respir Crit Care Med,* 162, 1330-4.

Juniper, E. F., O'Byrne, P. M., Guyatt, G. H., Ferrie, P. F. and King, D. R. (1999b) Development and validation of a queastionnaire to measure asthma control. *Eur Respir J,* 14, 902-7.

Juniper, E. F., Svensson, K., Mork, A. C. and Stahl, E. (2005) Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med,* 99 (5), 553-8.

Kang, M.-G., Kim, J.-Y., Jung, J.-W., Song, W.-J., Cho, S.-H., Min, K.-U. and Kang, H.-R. (2013) Lost to Follow-Up in Asthmatics Does Not Mean Treatment Failure: Causes and Clinical Outcomes of Non-Adherence To Outpatient Treatment In Adult Asthma. *Allergy Asthma Immunol Res,* 5 (6), 357-364.

Kelly, H. W. (2006) Pulmonary clinical pharamcy practice. *Annals of Pharmacotherapy,* 40 (7-8), 1407-1408.

Kendall, J. M. (2003) Designing a research project: randomised controlled trials and their principles. *Emergency Medicine Journal,* 20, 164-168.

Khachi, H. and Karikari, P. (2013) Impact of pharmacist-led asthma and COPD reviews in general practice. *Thorax,* 68(Suppl3), A110-A111.

Kharitonov, S. A., Gonio, F., Kelly, C., Meah, S. and Barnes, P. J. (2003) Reproducibility of exhaled nitric oxide measurements in healthy and asthmatic adults and children. *European Respiratory Journal,* 21 (3), 433-438.

Kinsman, R. A., Dirks, J. F. and Dahlem, N. W. (1980) Noncompliance to prescribed-as-neeed (PRN) medication use in asthma: usage patterns and patient characteristics. *J Psychosom Res,* 24, 97-107.

Knoell, D. L., Pierson, J. F., Marsh, C. B., Allen, J. N. and Pathak, D. S. (1998) Measurement of outcomes in adults receiving pharmaceutical care in a comprehensive asthma outpatient clinic. *Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy,* 18 (6), 1365-74.

Krauskopf, K. A., Sofianou, A., Goel, M. S., Wolf, M. S., Wilson, E. A. H., Martynenko, M. E., Halm, E. A., Leventhal, H., Feldman, J. M., Federman, A. D. and Wisnivesky, J. P. (2013) Depressive Symptoms, Low Adherence, and Poor Asthma Outcomes in the Elderly. *Journal of Asthma,* 50 (3), 260-266.

Kripalani, S., LeFevre, F., Phillips, C. O., Williams, M. V., Basaviah, P. and Baker, D. W. (2007) Deficits in Communication and Information Transfer Between Hospital-Based and Primary Care Physicians: Implications for Patient Safety and Continuity of Care. *JAMA,* 297 (8), 831-841.

Kritikos, V., Armour, C. L. and Bosnic-Anticevich, S. Z. (2007) Interactive small-group asthma education in the community pharmacy setting: a pilot study. *Journal of Asthma,* 44 (1), 57-64.

Kurtz, S., Silverman, J., Benson, J. and Draper, J. (2003) Marrying Content and Process in Clinical Method Teaching: Enhancing the Calgary–Cambridge Guides. *Academic Medicine,* 78 (8)**,** 802-809.

Laube, B. L., Janssens, H. M., de, F. H. F., Devadason, S. G., Dhand, R., Diot, P., Everard, M. L., Horvath, I., Navalesi, P., Voshaar, T., Chrystyn, H., European, R. S. and International, S. M. (2011) What the pulmonary specialist should know about the new inhalation therapies. *European Respiratory Journal,* 37 (6)**,** 1308-31.

Lavorini, F., Magnan, A., Dubus, J. C., Voshaar, T., Corbetta, L., Broeders, M., Dekhuijzen, R., Sanchis, J., Viejo, J. L., Barnes, P., Corrigan, C., Levy, M. and Crompton, G. K. (2008) Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respir Med,* 102 (4)**,** 593-604.

Lenney, J., Innes, J. A. and Crompton, G. K. (2000) Inappropriate inhaler use: assessment of use and patient preference of seven inhalation devices. *Respir Med,* 94**,** 496-500.

Levy, M. L., Hardwell, A., McKnight, E. and Holmes, J. (2013) Asthma patients' inability to use a pressurised metered-dose inhaler (pMDI) correctly correlates with poor asthma control as defined by the Global Initiative for Asthma (GINA) strategy: a retrospective analysis. *Primary Care Respiratory Journal,* 22 (4)**,** 406-411.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J. and Moher, D. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med,* 6 (7)**,** e1000100.

Lim, K. G., Rank, M. A., Li, J. T., Patel, A., Volcheck, G. W., Branda, M. E., Cabanela, R., Naessens, J. M., Shah, N. D., Wagie, A. and Beebe, T. (2010) How well does patient self-report predict asthma medication possession? Implications for medication reconciliation and adherence assessment. *Journal of Asthma,* 47 (8)**,** 878-82.

Lim, T., Kowalski, S. and Tan, K. (2012) Impact of Asthma Counseling by Pharmacist on Asthma Control and Medication Adherence in Asia. *The Journal of allergy and clinical immunology,* 129 (2)**,** AB125.

Lloyd, A., Price, D. and Brown, R. (2007) The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary Care Respiratory Journal,* 16 (1)**,** 22-27.

MacAdam, A. B. and Sherwood, J. (2011) An investigation into the provision of Medicines Use Reviews (MURs) by community pharmacists within Brighton and Hove Primary Care Trust. *int J Pharm Pract,* 19 ((Suppl 1))**,** 31.

Mangiapane, S., Schulz, M., Muhlig, S., Ihle, P., Schubert, I. and Waldmann, H. C. (2005) Community pharmacy-based pharmaceutical care for asthma patients. *Ann Pharmacother,* 39 (11)**,** 1817-22.

Mann, C. J. (2003) Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emergency Medicine Journal,* 20 (54-60).

Masoli, M., Weatherall, M., Holt, S. and Beasley, R. (2004) Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax,* 59 (1)**,** 16-20.

McLean, W., Gillis, J. and Waller, R. (2003) The BC Community Pharmacy Asthma Study: A study of clinical, economic and holistic outcomes influenced by an

asthma care protocol provided by specially trained community pharmacists in British Columbia. *Canadian Respiratory Journal,* 10 (4)**,** 195-202.
McNicholl, D. M. and Heaney, L. G. (2013) Reply: Assessing Adherence to Inhaled Medication in Difficult-to-Treat Asthma. *American Journal of Respiratory and Critical Care Medicine,* 188 (10)**,** 1263-1264.
Mehuys, E., Van Bortel, L., De Bolle, L., Van Tongelen, I., Annemans, L., Remon, J. P. and Brusselle, G. (2008) Effectiveness of pharmacist intervention for asthma control improvement. *Eur Respir J,* 31 (4)**,** 790-9.
Melani, A. S., Bonavia, M., Cilenti, V., Cinti, C., Lodi, M., Martucci, P., Serra, M., Scichilone, N., Sestini, P., Aliani, M., Neri, M. and Gruppo Educazionale Associazione Italiana Pneumologi, O. (2011) Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med,* 105 (6)**,** 930-8.
Melani, A. S., Zanchetta, D., Barbato, N., Sestini, P., Cinti, C., Canessa, P. A., Aiolfi, S., Neri, M. and Associazione, I. G. (2004) Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Annals of Allergy, Asthma, & Immunology,* 93 (5)**,** 439-46.
Menckeberg, T. T., Bouvy, M. L., Bracke, M., Kaptein, A. A., Leufkens, H. G., Raaijmakers, J. A. and Horne, R. (2008) Beliefs about medicines predict refill adherence to inhaled corticosteroids. *J Psychosom Res,* 64 (1)**,** 47-54.
Michils, A., Baldassarre, S. and Van Muylem, A. (2008) Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. *Eur Respir J,* 31 (3)**,** 539-46.
Moldrup, C., Stein, J. and Sondergaard, B. (2010) "Patients don't lie"; a view on adherence in asthma. *Pharmacy World & Science,* 32 (6)**,** 795-8.
Molimard, M., Raherison, C., Lignot, S., Depont, F., Abquelfath, A. and Moore, N. (2003) Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. *J Aerosol Med,* 16 (3)**,** 249-254.
Mora, P. A., Berkowitz, A., Contrada, R. J., Wisnivesky, J., Horne, R., Leventhal, H. and Halm, E. A. (2011) Factor structure and longitudinal invariance of the Medical Adherence Report Scale-Asthma. *Psychology & Health,* 26 (6)**,** 713-27.
Moullec, G., Gour-Provencal, G., Bacon, S. L., Campbell, T. S. and Lavoie, K. L. (2012) Efficacy of interventions to improve adherence to inhaled corticosteroids in adult asthmatics: Impact of using components of the chronic care model. *Respiratory Medicine,* 106 (9)**,** 1211-1225.
Munzenberger, P. J. and Hill, M. J. (2007) Impact of an asthma-specific questionnaire on problem identification and clinical and economic outcomes in ambulatory patients with persistent asthma. *Journal of the American Pharmacists Association,* 47 (2)**,** 147-155.
Murphy, A. (2014) Make asthma SIMPLE for your patients. *Pharmaceutical Journal,* 292 (7809/10)**,** 515.
Murphy, A., Knight, H., Bennett, J., Elander, J. and Langton, H. (2012a) Can a community pharmacy-based intervention for people with asthma fully integrated with other community services lead to improved clinical outcomes? *International Journal of Pharmacy Practice,* 20 (Suppl 2)**,** 62-63.
Murphy, A. C., Proeschal, A., Brightling, C. E., Wardlaw, A. J., Pavord, I., Bradding, P. and Green, R. H. (2012b) The relationship between clinical outcomes and

medication adherence in difficult-to-control asthma. *Thorax,* 67 (8), 751-753.
Naik-Panvelkar, P., Armour, C., Rose, J. M. and Saini, B. (2012) Patient preferences for community pharmacy asthma services: A discrete choice experiment. *Pharmacoeconomics,* 30 (10), 961-976.
Nathan, R. A., Sorkness, C. A., Kosinski, M., Schatz, M., Li, J. T., Marcus, P., Murray, J. J. and Pendergraft, T. B. (2004) Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol,* 113 (1), 59-65.
National Institute for Health and Care Excellence (2009) *NICE CG76. Medicines adherence, involving patients in decisions about prescribed medicines and supporting adherence.* Manchester, UK: National Institute for Health and Care Excellence.
National Institute for Health and Care Excellence (2013) *NICE quality standard 25: Quality standard for asthma.* Manchester, UK: National Institute for Health and Care Excellence.
National Institute for Health and Clinical Excellence (2008) *Guide to the Methods of Technology Appraisal.* London, UK: National Institute for Health and Clinical Excellence.
Newman, S., Steed, K., Hooper, G., Källén, A. and Borgström, L. (1995) Comparison of Gamma Scintigraphy and a Pharmacokinetic Technique for Assessing Pulmonary Deposition of Terbutaline Sulphate Delivered by Pressurized Metered Dose Inhaler. *Pharmaceutical Research,* 12 (2), 231-236.
Newman, S. P. (1985) Aerosol Deposition Considerations in Inhalation Therapy. *Chest,* 88 (2 Supplement), 152S-160S.
NHS England (2013) *2013/14 NHS Standard Contract for Respiratory: Severe Asthma (Adults).* London, UK: NHS England.
Nikander, K. (2010) Challenges and opportunities in respiratory drug delivery devices. *Expert Opinion on Drug Delivery,* 7 (11), 1235-8.
Nsour, W. M., Alldred, A., Corrado, O. J. and Chrystyn, H. (2001) Measurement of peak inhalation rates with an In-Check Meter®to identify an elderly patient's ability to use a Turbuhaler®. *Respiratory Medicine,* 95 (12), 965-968.
O'Neill, S., Sweeney, J., Patterson, C. C., Menzies-Gow, A., Niven, R., Mansur, A. H., Bucknall, C., Chaudhuri, R., Thomson, C., Brightling, C. E., O'Neill, C. and Heaney, L. G. (2014) The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax*, Published Online First: 10th June 2014. Doi:10.1136/thoraxjnl-2013-204114.
Office for National Statistics (2013) *Population Estimates for UK, England and Wales, Scotland and Northern Ireland, mid 2012.* Newport, UK: Office for National Statistics. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-319259 (Accessed 24th September 2013).
Osterberg, L. and Blaschke, T. (2005) Adherence to Medication. *N Engl J Med,* 353 (5), 487-97.
Ovchinikova, L., Smith, L. and Bosnic-Anticevich, S. (2011) Inhaler technique maintenance: gaining an understanding from the patient's perspective. *Journal of Asthma,* 48 (6), 616-24.
Palander, A., Mattila, T., Karhu, M. and Muttonen, E. (2000) In vitro Comparison of Three Salbutamol-Containing Multidose Dry Powder Inhalers. *Clinical Drug Investigation,* 20 (1), 25-33.

Park, J., Jackson, J., Skinner, E., Ranghell, K., Saiers, J. and Cherney, B. (2010) Impact of an adherence intervention program on medication adherence barriers, asthma control, and productivity/daily activities in patients with asthma. *Journal of Asthma,* 47 (10), 1072-7.

Patel, M. R., Valerio, M. A., Janevic, M. R., Gong, Z. M., Sanders, G., Thomas, L. J. and Clark, N. M. (2013) Long-Term Effects of Negotiated Treatment Plans on Self-Management Behaviors and Satisfaction with Care Among Women with Asthma. *Journal of Asthma,* 50 (1), 82-89.

Pauley, T. R., Magee, M. J. and Cury, J. D. (1995) Pharmacist-managed, physician-directed asthma management program reduces emergency department visits. *Annals of Pharmacotherapy,* 29 (1), 5-9.

Petkova, V. B. (2008) Pharmaceutical care for asthma patients: a community pharmacy-based pilot project. *Allergy Asthma Proc,* 29 (1), 55-61.

Petrie, J. L. and Segal, A. R. (2010) Clinical pharmacy services provided to asthma patients in a school-based clinic. *American Journal of Health-System Pharmacy,* 67 (3), 185-189.

Pharmaceutical Services Negotiating Committee (2013) *Guidance on the medicines use review service.* London, UK: Pharmaceutical Services Negotiating Committee. Available from: http://psnc.org.uk/wp-content/uploads/2013/06/MUR-Guidance-Oct-2013.pdf (Accessed 3rd Septembr 2014).

Pizzi, L. T., Menz, J. M., Graber, G. R. and Suh, D. (2001) From product dispensing to patient care: the role of the pharmacist in providing pharmaceutical care as part of an integrated disease management approach. *Disease Management,* 4 (4), 143-154.

Ponieman, D., Wisnivesky, J. P., Leventhal, H., Musumeci-Szabo, T. J. and Halm, E. A. (2009) Impact of positive and negative beliefs about inhaled corticosteroids on adherence in inner-city asthmatic patients. *Annals of Allergy, Asthma, & Immunology,* 103 (1), 38-42.

Portlock, J., Holden, M. and Patel, S. (2009) A Community Pharmacy Asthma MUR Project in Hampshire and the Isle of Wight. *Pharmaceutical Journal,* 282, 109-112.

Prescribing and Primary Care team (2013) *General Pharmaceutical Services in England - 2003-04 to 2012-13.* Health & Social Care Information Centre. Available from: http://www.hscic.gov.uk/catalogue/PUB12683 (Accessed 22nd September 2014).

Press, V. G., Arora, V. M., Shah, L. M., Lewis, S. L., Charbeneau, J., Naureckas, E. T. and Krishnan, J. A. (2012) Teaching the Use of Respiratory Inhalers to Hospitalized Patients with Asthma or COPD: a Randomized Trial. *Journal of General Internal Medicine,* 27 (10), 1317-1325.

Price, D., Bosnic-Anticevich, S., Briggs, A., Chrystyn, H., Rand, C., Scheuch, G. and Bousquet, J. (2013) Inhaler competence in asthma: Common errors, barriers to use and recommended solutions. *Respiratory Medicine,* 107 (1), 37-46.

Put, C., van den Bergh, O., Lemaigre, V., Demedts, M. and Verleden, G. (2003) Evaluation of an individualised asthma programme directed at behavioural change. *European Respiratory Journal,* 21 (1), 109-115.

Rathan Shyam, M., Jyothi, D., Prasad, T. S. D., Venkata Subbaiah, M., Ravindra Reddy, K. and Babu, S. C. (2013) Role of clinical pharmacist in impact of patient counselling in asthmatic patients. *Journal of Global Trends in Pharmaceutical Sciences,* 4 (2), 1111-1117.

Reddel, H. K., Taylor, D. R., Bateman, E. D., Boulet, L. P., Boushey, H. A., Busse, W. W., Casale, T. B., Chanez, P., Enright, P. L., Gibson, P. G., de Jongste, J. C., Kerstjens, H. A., Lazarus, S. C., Levy, M. L., O'Byrne, P. M., Partridge, M. R., Pavord, I. D., Sears, M. R., Sterk, P. J., Stoloff, S. W., Sullivan, S. D., Szefler, S. J., Thomas, M. D. and Wenzel, S. E. (2009) An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med,* 180 (1)**,** 59-99.

Resnick, D. J., Gold, R. L., Lee-Wong, M., Feldman, B. R., Ramakrishnan, R. and Davis, W. J. (1996) Physicians' metered dose inhaler technique after a single teaching session. *Annals of Allergy, Asthma, & Immunology,* 76 (2)**,** 145-8.

Roberts, N. J., Robinson, D. S. and Partridge, M. R. (2006) How is difficult asthma managed? *European Respiratory Journal,* 28**,** 968-973.

Roland, M. and Torgerson, D. J. (1998) Understanding controlled trials: What are pragmatic trials? *BMJ,* 316 (7127)**,** 285.

Roller, L. and Gowan, J. (2013) Asthma and adherence. *Australian Journal of Pharmacy,* 94**,** 62-68.

Roy, A., Battle, K., Lurslurchachai, L., Halm, E. A. and Wisnivesky, J. P. (2011) Inhaler device, administration technique, and adherence to inhaled corticosteroids in patients with asthma. *Primary Care Respiratory Journal,* 20 (2)**,** 148-54.

Royal College of Physicians (2014) *Why asthma still kills: the national review of asthma deaths (NRAD) confidential enquiry report.* London: RCP.

Ryan, D., Murphy, A., Stallberg, B., Baxter, N. and Heaney, L. G. (2013) 'SIMPLES': a structured primary care approach to adults with difficult asthma. *Primary Care Respiratory Journal,* 22 (3)**,** 365-373.

Saini, B., Filipovska, J., Bosnic-Anticevich, S., Taylor, S., Krass, I. and Armour, C. (2008) An evaluation of a community pharmacy-based rural asthma management service. *Australian Journal of Rural Health,* 16 (2)**,** 100-8.

Saini, B., Krass, I., Smith, L., Bosnic-Anticevich, S. and Armour, C. (2011a) Role of community pharmacists in asthma - Australian research highlighting pathways for future primary care models. *Australasian Medical Journal,* 4 (4)**,** 190-200.

Saini, B., LeMay, K., Emmerton, L., Krass, I., Smith, L., Bosnic-Anticevich, S., Stewart, K., Burton, D. and Armour, C. (2011b) Asthma disease management-Australian pharmacists' interventions improve patients' asthma knowledge and this is sustained. *Patient Education & Counseling,* 83 (3)**,** 295-302.

Saini, B., Smith, L., Armour, C. and Krass, I. (2006) An Educational Intervention to Train Community Pharmacists in Providing Specialized Asthma Care. *American Journal of Pharmaceutical Education,* 70 (5)**,** 118.

Santos, D. d. O., Martins, M. C., Cipriano, S. L., Pinto, R. M. C., Cukier, A. and Stelmach, R. (2010) Pharmaceutical care for patients with persistent asthma: assessment of treatment compliance and use of inhaled medications. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisilogia,* 36 (1)**,** 14-22.

Shams, M. R. and Fineman, S. M. (2014) Asthma adherence: how can we help our patients do it better? *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology,* 112 (1)**,** 9-12.

Shaw, D. E., Berry, M. A., Thomas, M., Green, R. H., Brightling, C. E., Wardlaw, A. J. and Pavord, I. D. (2007) The use of exhaled nitric oxide to guide asthma

management: a randomized controlled trial. *Am J Respir Crit Care Med,* 176 (3), 231-7.
Simpson, M. D., Burton, D. L., Burton, M. A., Gissing, P. M. and Bowman, S. L. (2004) Pharmaceutical Care: Impact on Asthma Medication Use. *Journal of Pharmacy Practice and Research,* 34 (1), 26-29.
Slejko, J. F., Ho, M., Anderson, H. D., Nair, K. V., Sullivan, P. W. and Campbell, J. D. (2014) Adherence to statins in primary prevention: yearly adherence changes and outcomes. *Journal of Managed Care Pharmacy,* 20 (1), 51--57.
Smith, A. D., Cowan, J. O., Brassett, K. P., Filsell, S., McLachlan, C., Monti-Sheehan, G., Peter Herbison, G. and Robin Taylor, D. (2005a) Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med,* 172 (4), 453-9.
Smith, A. D., Cowan, J. O., Brassett, K. P., Herbison, P. and Taylor, D. R. (2005b) Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med,* 352 (21), 2163-73.
Smith, L., Bosnic-Anticevich, S. Z., Mitchell, B., Saini, B., Krass, I. and Armour, C. (2007) Treating asthma with a self-management model of illness behaviour in an Australian community pharmacy setting. *Social Science & Medicine,* 64 (7), 1501-1511.
Sofianou, A., Martynenko, M., Wolf, M. S., Wisnivesky, J. P., Krauskopf, K., Wilson, E. A. H., Goel, M. S., Leventhal, H., Halm, E. A. and Federman, A. D. (2013) Asthma Beliefs Are Associated with Medication Adherence in Older Asthmatics. *Journal of General Internal Medicine,* 28 (1), 67-73.
Stewart, M. A. (1995) Effective physician-patient communication and health outcomes: a review. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne,* 152 (9), 1423-1433.
Stiegler, K. A., Yunker, N. S. and Crouch, M. A. (2003) Effect of pharmacist counseling in patients hospitalized with acute exacerbation of asthma. *American Journal of Health-System Pharmacy,* 60 (5), 473-6.
Strandbygaard, U., Thomsen, S. F. and Backer, V. (2010) A daily SMS reminder increases adherence to asthma treatment: a three-month follow-up study. *Respir Med,* 104 (2), 166-71.
Suissa, S. and Ernst, P. (2001) Inhaled corticosteroids: Impact on asthma morbidity and mortality. *Journal of Allergy and Clinical Immunology,* 107 (6), 937-944.
Suissa, S., Ernst, P., Benayoun, S., Baltzan, M. and Cai, B. (2000) Low-Dose Inhaled Corticosteroids and the Prevention of Death from Asthma. *New England Journal of Medicine,* 343 (5), 332-336.
Svedsater, H., Dale, P., Garrill, K., Walker, R. and Woepse, M. (2013) Qualitative assessment of attributes and ease of use of the ELLIPTA dry powder inhaler for delivery of maintenance therapy for asthma and COPD. *BMC Pulmonary Medicine,* 13 (1), 72.
Sweeney, J., Brightling, C. E., Menzies-Gow, A., Niven, R., Patterson, C. C. and Heaney, L. G. (2012) Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry. *Thorax,* 67 (754-756).
Takemura, M., Kobayashi, M., Kimura, K., Mitsui, K., Masui, H., Koyama, M., Itotani, R., Ishitoko, M., Suzuki, S., Aihara, K., Matsumoto, M., Oguma, T., Ueda, T., Kagioka, H. and Fukui, M. (2010) Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma. *Journal of Asthma,* 47 (2), 202-8.
Takemura, M., Mitsui, K., Ido, M., Matsumoto, M., Koyama, M., Inoue, D., Takamatsu, K., Itotani, R., Ishitoko, M., Suzuki, S., Aihara, K., Sakuramoto, M., Kagioka, H.

and Fukui, M. (2012) Impact of a Network System for Providing Proper Inhalation Technique by Community Pharmacists. *Journal of Asthma,* 49 (5), 535-541.

The Cambridge Consortium (2012) *Evaluation of inhaler technique improvement project.* Cambridge, UK: Cambridge Inst. for Research Education and Management (CiREM).

The EuroQol Group (1990) EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy,* 16 (3), 199-208.

To, K. W., Lee, W. M., Choi, K. C., Yu, D., Chau, J. and Lee, I. (2013) Educational and supportive interventions for improving adherence to inhalation therapy in people with chronic respiratory diseases: A systematic review protocol. *JBI Database of Systematic Reviews & Implementation Reports,* 11 (1), 3290345.

Toumas, M., Basheti, I. A. and Bosnic-Anticevich, S. Z. (2009) Comparison of small-group training with self-directed internet-based training in inhaler techniques. *American Journal of Pharmaceutical Education,* 73 (5).

Usmani, O. S., Biddiscombe, M. F. and Barnes, P. J. (2005) Regional Lung Deposition and Bronchodilator Response as a Function of β2-Agonist Particle Size. *American Journal of Respiratory and Critical Care Medicine,* 172 (12), 1497-1504.

Vaidya, V., Tak, S. and Hong, S. H. (2013) Impact of patient cost sharing on medication adherence among asthmatic patients on dual-controller therapy. *Journal of Pharmaceutical Health Services Research,* 4 (4), 227-233.

van den Berg, M. and Donyai, P. (2010) A retrospective audit of medicines use review forms. *int J Pharm Pract,* 18 ((Suppl 1)), B33-B34.

van Es, S. M., Nagelkerke, A. F., Colland, V. T., Scholten, R. J. P. M. and Bouter, L. M. (2001) An intervention programme using the ASE-model aimed at enhancing adherence in adolescents with asthma. *Patient Education and Counseling,* 44 (3), 193-203.

Voshaar, T., Spinola, M., Linnane, P., Campanini, A., Lock, D., Lafratta, A., Scuri, M., Ronca, B. and Melani, A. S. (2013) Comparing Usability of NEXThaler with Other Inhaled Corticosteroid/Long-Acting beta-Agonist Fixed Combination Dry Powder Inhalers in Asthma Patients. *J Aerosol Med Pulm Drug Deliv,* Published ahead of print, doi:10.1089/jamp.2013.1086.

Wang, K. Y., Chian, C. F., Lai, H. R., Tarn, Y. H. and Wu, C. P. (2010) Clinical pharmacist counseling improves outcomes for Taiwanese asthma patients. *Pharmacy World & Science,* 32 (6), 721-9.

Watanabe, T., Ohta, M., Murata, M. and Yamamoto, T. (1998) Decrease in emergency room or urgent care visits due to management of bronchial asthma inpatients and outpatients with pharmaceutical services. *Journal of Clinical Pharmacy and Therapeutics,* 23 (4), 303-309.

Waterfield, J. and Dhir, A. (2011) An exploration of the views of community pharmacists on the relationship between Medicines Use Reviews (MURs) and public health. *int J Pharm Pract,* 19 (Suppl 2), 68-69.

Weinberger, M., Murray, M. D., Marrero, D. G., Brewer, N., Lykens, M., Harris, L. E., Seshadri, R., Caffrey, H., Roesner, J. F., Smith, F., Newell, A. J., Collins, J. C., McDonald, C. J. and Tierney, W. M. (2002) Effectiveness of pharmacist care for patients with reactive airways disease: a randomized controlled trial. *JAMA,* 288 (13), 1594-602.

Wener, R. R. and Bel, E. H. (2013) Severe refractory asthma: an update. *Eur Respir Rev,* 22 (129), 227-35.

Wenzel, S. E. (2012) Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med,* 18 (5)**,** 716-725.

WIlliams, I., Churchill, D., Anderson, J., Boffito, M., Bower, M., Cairns, G., Cwynarski, K., Edwards, S., Fidler, S., Fisher, M., Freedman, A. and Geretti, A. M. (2012) British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012. *HIV Medicine,* 13 (Suppl 2)**,** 1-85.

Williams, L. K., Peterson, E. L., Wells, K., Ahmedani, B. K., Kumar, R., Burchard, E. G., Chowdhry, V. K., Favro, D., Lanfear, D. E. and Pladevall, M. (2011) Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *Journal of Allergy & Clinical Immunology,* 128 (6)**,** 1185-1191.e2.

Williams, L. K., Peterson, E. L., Wells, K., Campbell, J., Wang, M., Chowdhry, V. K., Walsh, M., Enberg, R., Lanfear, D. E. and Pladevall, M. (2010) A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. *Journal of Allergy & Clinical Immunology,* 126 (2)**,** 225-31, 231.e1-4.

Wittbrodt, E., Koval, P., Raissy, H. H. and Nichols, J. (2006) Treatment Algorithms from the Pharmacist Perspective. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy,* 26 (9P2)**,** 203S-206S.

Wojtczak, H. A., Wachter, A. M., Lee, M., Burns, L. and Yusin, J. S. (2012) Understanding the relationship among pharmacoadherence measures, asthma control test scores, and office-based spirometry. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology,* 109 (2)**,** 103-107.

Woodcock, A. A., Bagdonas, A., Boonsawat, W., Gibbs, M. R., Bousquet, J. and Bateman, E. D. (2007) Improvement in asthma endpoints when aiming for total control: salmeterol/fluticasone propionate versus fluticasone propionate alone. *Primary Care Respiratory Journal,* 16 (3)**,** 155-61.